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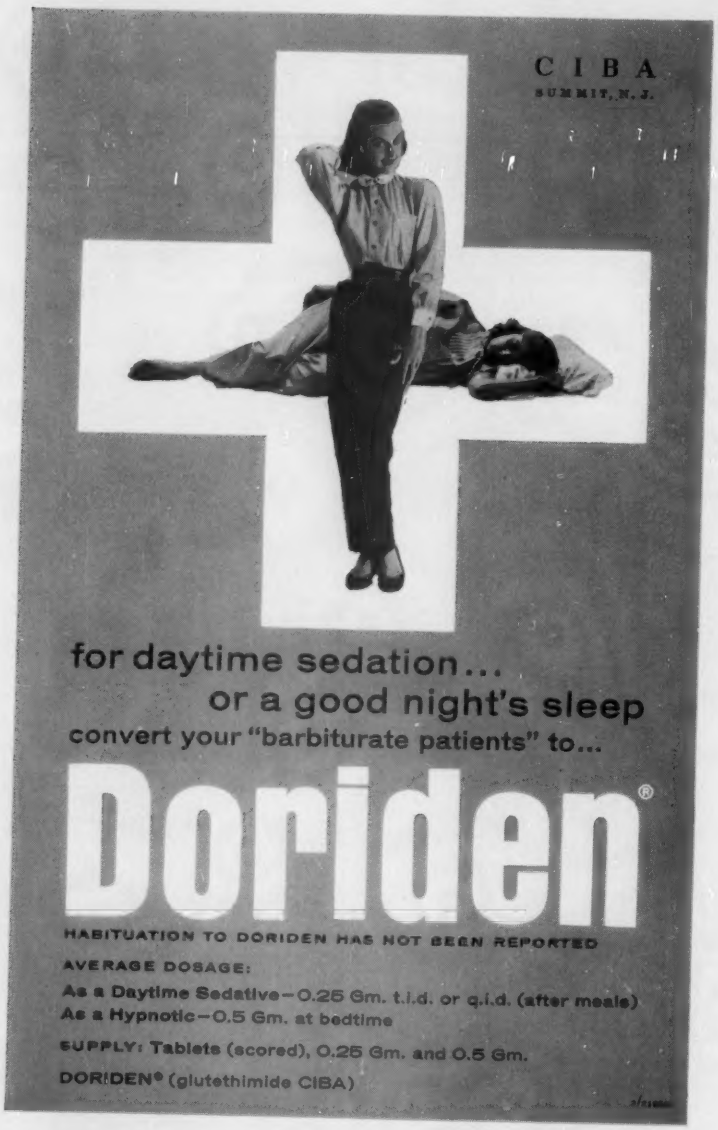
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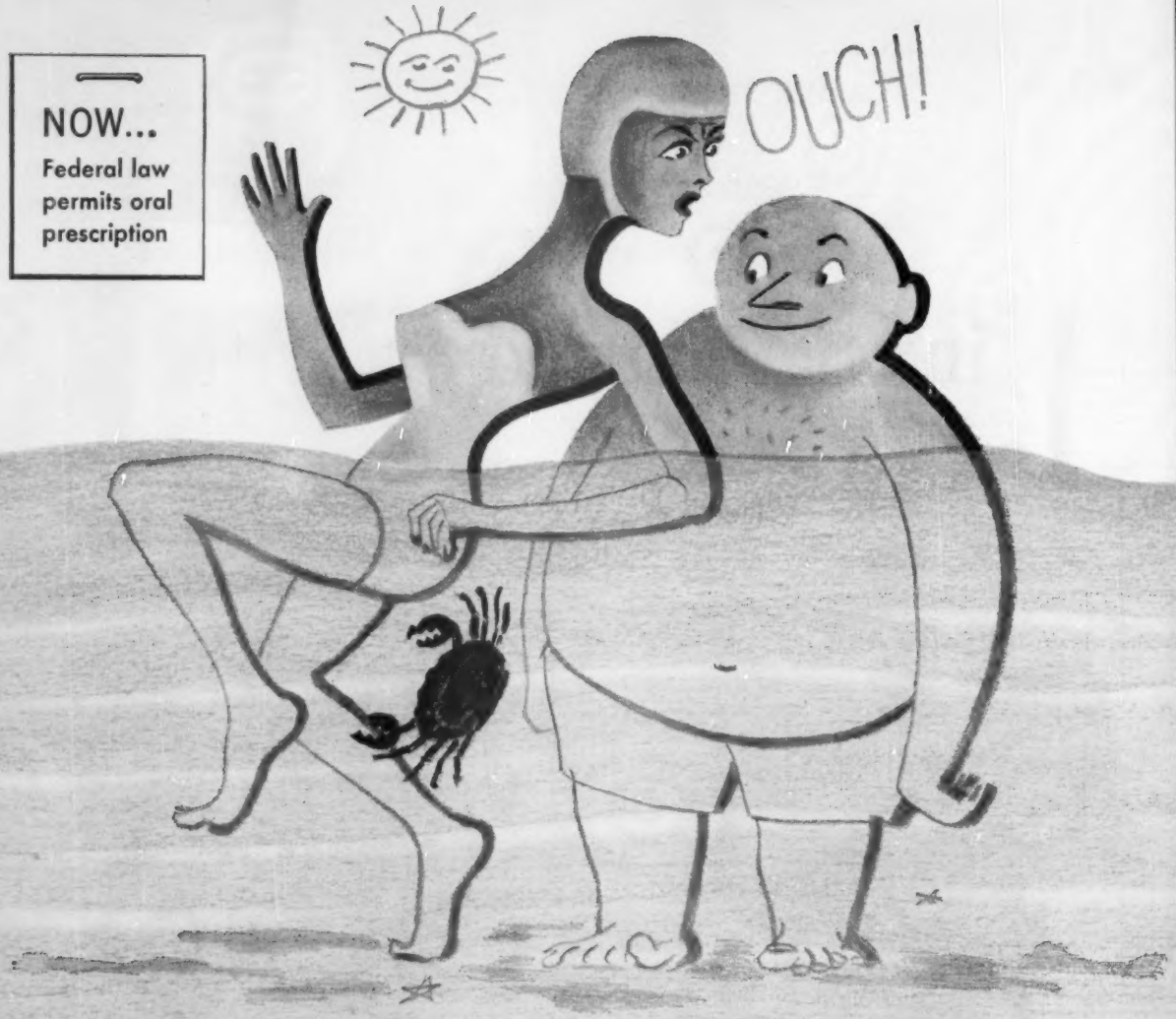

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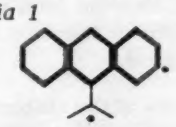

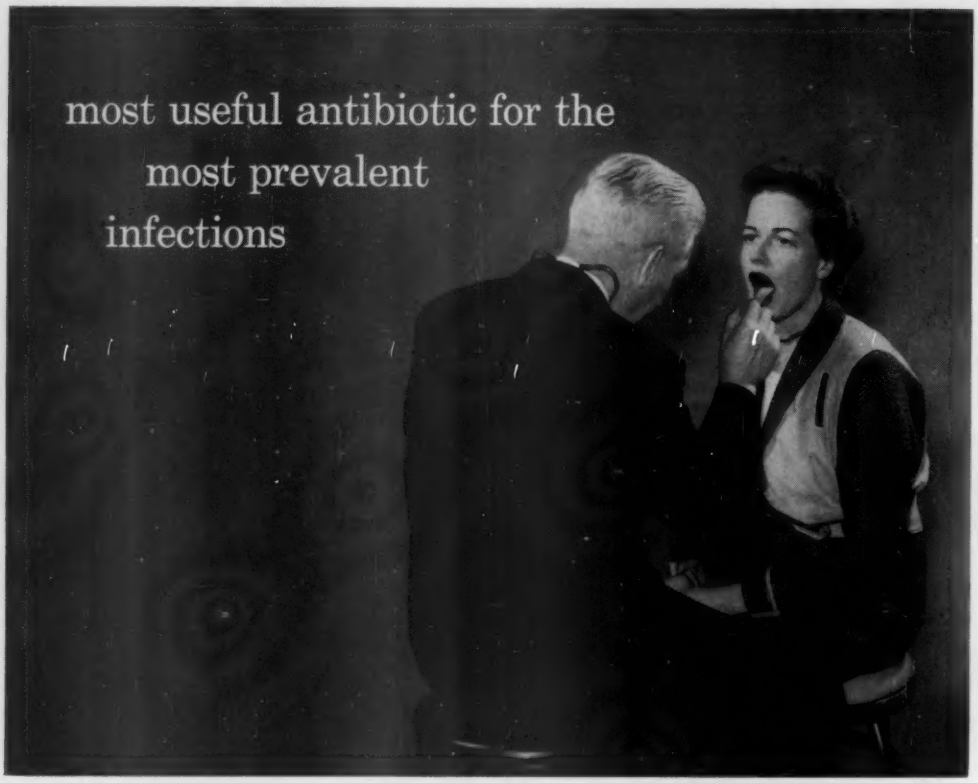

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Volume 253 NOVEMBER 24, 1955 Number 21

DISCREPANCIES BETWEEN SUBJECTIVE AND OBJECTIVE RESPONSES TO MITRAL COMMISSUROTOMY*

GORDON G. BERGY, M.D.,† AND ROBERT A. BRUCE, M.D.‡

SEATTLE, WASHINGTON

THE importance of critical and objective evaluation of any new therapy is well recognized by the medical profession. The need for applying this principle to the appraisal of mitral commissurotomy has been emphatically indicated by Soloff and Zatuchni,[1] who have been impressed by the morbidity and mortality resulting from this form of treatment. Their findings are contrary to the enthusiastic reports of surgeons that are based on subjective evaluation of their patients.

Objective evaluation of surgical therapy is difficult because of variations in the natural history of rheumatic heart disease as influenced by respiratory infections, arrhythmias, thromboembolism or recurrences of rheumatic activity, any of which may precipitate heart failure. Patients surviving these complications may show no apparent change or may exhibit cardiac dilatation or progressive valvular disease.

Furthermore, the postcommissurotomy syndrome often obscures the initial result in patients undergoing valve surgery.[2] In addition, the clinical and laboratory evaluation of a small group of patients not operated on and followed for a year has shown equal improvement in all but those with Class 4 disease.[3]

Since objective evaluation of cardiorespiratory responses to a standard exercise test has been used in this laboratory for both preoperative and postoperative study of mitral stenosis, it has been possible to evaluate the effects of surgery more critically.[4]

MATERIAL

All patients surviving mitral-valve surgery were approached by means of a questionnaire. Thirty-one patients (60 per cent) were able to return to the laboratory four to thirty-eight months (average of twenty-one) after operation. Eighty-seven per cent were seen over twelve months after operation.

*From the Department of Medicine, University of Washington School of Medicine.

†Assistant in medicine, University of Washington School of Medicine and King County Hospital; trainee of the National Heart Institute, 1954-1955.

‡Associate professor of medicine, University of Washington School of Medicine; consultant in cardiology, King County Hospital.

Patients not included in the study were patients who could no longer be communicated with, too ill or financially unable to travel long distances to Seattle. No attempt was made to select patients according to their response to surgery. To evaluate surgical, rather than medical, therapy, final postoperative findings have been compared with final preoperative data obtained after prolonged medical management.

METHODS

Routine history and physical examination, fluoroscopy and chest roentgenograms, 12-lead electrocardiogram and vital capacity were obtained before and after operation on each patient. Additional medical and social history, including reviews of the work and recreational records, were compared with findings from the questionnaire postoperatively.

The standard exercise test[4] was done, frequently several times, before and after surgery. This required the patient to walk for ten minutes at 1.73 miles per hour on a 10 per cent grade. Whenever the symptoms were too severe, so that patients were unable to walk for ten minutes, the exact duration of effort was recorded and used to estimate the performance index. Observations were made each minute of heart rate, blood pressure, respiratory efficiency and precordial electrocardiogram. A physical-fitness index of over-all cardiorespiratory performance was calculated from the following formula:

$$\text{P.F.I.} = \frac{\text{Endurance x respiratory efficiency x 100}}{\text{Cumulative 3-minute recovery heart rate}}.$$

RESULTS

Replies to the Questionnaire

Twenty-nine out of 31 patients classified themselves as "better," 1 was "the same," and 1 gave no answer (Table 1). All would have been willing to have the operation again under similar circumstances.

Seven reported "relapses," with symptoms due either to heart failure or to manifestations of the postcommissurotomy syndrome.

Although 11 patients classified their activity as "unlimited," most of these avoided heavy lifting, climbing hills or stairs, scrubbing or carrying heavy packages. Fifteen still required daytime periods of bed rest ranging from half an hour to twelve hours in duration. All but 4 still require some type of medical therapy: 23 take some form of digitalis, 5 quinidine, 2 (who are now hypertensive) receive *R. serpentina,* and 4 (who have had recent active rheumatic carditis) receive daily penicillin prophylaxis by mouth.

TABLE 1. *31 Replies to Questionnaires.*

RESULT OF OPERATION	NO. OF PATIENTS	PERCENTAGE
Patient's attitudes:		
Feeling better	29	94
Feeling same	1	3
Question not answered	1	3
Willing to have operation again	31	100
Patient's record		
Postoperative relapse	7	23
Persistent limitation	20	65
Daily rest required	15	48
Medical therapy:		
Digitalis	23	74
Quinidine	5	16
R. serpentina	2	6

Preoperative and postoperative scores on the Cornell Medical Index[5] were available on 18 patients.

TABLE 2. *Frequency of Symptoms.*

SYMPTOM	NO. OF CASES
Dyspnea	19
Fatigue	15
Chest pain	10
Palpitation	10
Cough	7
Orthopnea	5
Weakness	5
Leg pain or cramps	5
Dizziness	3

The average number of affirmative responses decreased from 39 to 31 after surgery, with a decrease of 9 to 7 positive replies in the mood and affect classifications. In several cases there were higher scores in both organic and emotional groups afer operation.

Symptoms

The most common limiting symptoms in daily life were exertional dyspnea for 19 and ease of fatigue for 15 patients (Table 2). Ten still experienced chest pain (nonincisional), which was usually related to exertion. Cough, orthopnea, weakness and leg pain on exertion were still experienced by a significant number of patients.

Twenty-six out of 29 patients who said they were "better" were asked to explain this opinion in terms of decrease or abolition of specific symptoms. Sixteen cited decrease in awareness of dyspnea, 8 decrease in fatigue, and 7 absence of cough or hemoptysis. Three patients, however, could specify no tangible change.

Work Record

Whereas 17 patients stated that they could do full-time work before surgery, 14 of these had slight or moderate limitations with exertion (Table 3). After operation 24 patients could do full-time work, and 15, instead of 3, had no limitations with effort.

TABLE 3. *Work Record.*

WORK STATUS	NO. OF PATIENTS	
	BEFORE OPERATION	AFTER OPERATION
Totally disabled	11	3
Part-time light work	4	4
Full-time work, with moderate limitation of exertion	11	3
Full-time work, with slight limitation of exertion	3	6
Full-time work, with no limitations	3	15

Three patients had to change to easier jobs, however. Only 3, instead of 11, patients were totally disabled, and the number of those able to do part-time work was unchanged.

Twenty-five patients were queried about recreational activities, and only 9 had sufficient reserve after the day's work to attend movies, make social calls or go for a car ride. Only 5 have ever danced or engaged in sports such as bowling or golf, and only 1 has participated in a competitive sport (baseball) since operation.

Signs

The frequency of murmurs is shown in Table 4. In no case had the murmur of mitral stenosis entirely disappeared, though intensity was usually decreased. Seven patients had early decrescendo diastolic mur-

TABLE 4. *Frequency and Types of Murmurs.*

TYPE OF MURMUR	NO. OF PATIENTS	
	BEFORE OPERATION	AFTER OPERATION
Mitral stenosis	31	31
Mitral insufficiency	13	15
Decrescendo diastolic murmurs along left sternal border	7	11
Tricuspid insufficiency	1	2
Aortic stenosis	0	2

murs along the left sternal border preoperatively. This murmur disappeared in 6 patients but was heard for the first time in 10 others after operation. In some cases improved cardiac output may have "unmasked" a previously unrecognized murmur of aortic insufficiency. In others this was considered a Graham-Steell murmur.

The frequency of *mitral insufficiency,* as determined by auscultation, has increased from 13 to 15 patients; after surgery it disappeared in 3 and appeared for the first time in 5 others, and the intensity definitely increased in 1 patient.

A slightly enlarged liver was noted in 4 patients, minimal distention of neck veins and rales in ?, and edema in 1. On the basis of these findings postoperatively and evidence of either pulmonary congestion by fluoroscopy or prolonged circulation time, 5 patients were considered to exhibit minor degrees of heart failure. Only 1 of these patients showed more marked signs on examination after the exercise test.

TABLE 5. *Responses to Standard Exercise.*

DATUM*	FREQUENCY OF RESPONSE	
	BEFORE OPERATION	AFTER OPERATION
	%	%
Endurance (10 min.)	68	84
Physical-fitness index (13-26)	29	48
Heart rate (3-min. recovery <366)	65	84
Respiratory efficiency (>4.1 vol. per cent)	35	23
Blood-pressure response†	6	13

*Normal values in parentheses.
†Systolic-pressure increase of 10-35 mm. Hg.

Electrocardiographic Findings

The frequency of atrial fibrillation decreased from 16 to 11 patients. One now has atrial flutter, and the remaining 19 have sinus rhythm. Only 2 now have right-sided heart-strain patterns whereas preoperatively there were 9 with right-sided and 2 with combined strain.

Exercise-Tolerance Test

Twenty-nine patients had sufficient cardiopulmonary reserve to justify exercise-tolerance tests. Twenty-six (84 per cent) were able to walk for ten minutes, whereas only 21 had been able to do so preoperatively (Table 5). Normal respiratory efficiency of 4.1 vol. per cent was achieved by only 7 (23 per cent) as compared to 10 before surgery. Fifteen now achieved a physical-fitness-index score in the normal range (13 to 26) in contrast to 9 previously.

TABLE 7. *Symptoms and Signs during Standard Exercise-Tolerance Test.*

SYMPTOM OR SIGN	NO. OF PATIENTS	
	BEFORE OPERATION	AFTER OPERATION
Dyspnea:		
Slight	3	14
Moderate	10	7
Severe	10	0
Fatigue:		
Slight	2	16
Moderate	6	3
Severe	13	2
Signs of heart failure	7	1

Mean values of the physiologic measurements of the exercise test (Table 6) showed a slight increase in endurance from 8.0 to 9.6 minutes of walking, a slight decrease in respiratory efficiency from 3.9 to 3.8 vol. per cent, and a decrease in three-minute-recovery heart rate from 351 to 313 (upper limit of normal 360). The physical-fitness index of over-all cardiorespiratory performance rose from 9.4 to 12.1 (range, 3.0 to 16.9). Maximum systolic blood pressures on exercise increased from 137 to 153 mm. of mercury toward normal values. The principal symptoms experienced during exercise were dyspnea and fatigue (Table 7). Chest pain, dizziness and weakness or pain in the legs were rarely noted. Preoperatively, 20 patients had moderate or severe dyspnea (accompanied by acute signs of heart failure in 4), whereas only 7 had moderate dyspnea without signs of cardiac insufficiency after operation. Many still have slight dyspnea, however. The number of patients with severe or moderate fatigue decreased from 19 to 5.

TABLE 6. *Mean Values of Standard Exercise-Tolerance Test.*

EVALUATION	ENDURANCE	RESPIRATORY EFFICIENCY	MAXIMUM EXERCISE HEART RATE	MAXIMUM SYSTOLIC BLOOD PRESSURE	3-MIN.-RECOVERY HEART RATE	PHYSICAL-FITNESS INDEX
	min.	*vol. per cent*		*mm. Hg.*		
Final preoperative	8.0	3.94	162	137	351	9.4
Current postoperative	9.64	3.80	153	153	313	12.1

Pulmonary Function

The mean vital capacity fell from 78 to 73 per cent of the predicted normal values. The half-second expiratory volume (not measured preoperatively)

ranged from 10 to 89 per cent, with a mean of 58 per cent (lower limit of normal, 60 per cent).

Discussion

Although questionnaires reveal that 29 of 31 patients consider themselves "better" as a result of mitral-valve surgery, 16 had higher, 6 the same, and 7 lower physical-fitness-index scores. Thus, there was a correlation with objective evidence in only 55 per cent of the patients. The patient who said he was "the same" had a lower physical-fitness index postoperatively, whereas the one who gave no answer (and really believed she was worse) had a higher index. Most patients still need some form of medical therapy, and half still need daytime periods of bed rest. These two facts, in contrast to subjective opinions, correlate with objective findings on physical examination and standard exercise-tolerance tests. Hence, for some patients the term "better" describes a change in attitude toward their disease and disability, rather than improvement in cardiorespiratory function.

Changes in attitude may be due to the interaction of several factors. Certainly, the enthusiastic and positive approach by the surgeon is important, especially when it is coupled with a belief by the patient that improvement will ensue. Once surgery has been accomplished, the patient is emboldened to change his way of life. The careful medical supervision, with a close doctor-patient relation before, during and immediately after operation, undoubtedly brings about subjective as well as objective benefits.

The most important effects of surgery were the decreased intensity and frequency of dyspnea and fatigue after effort. These changes were corroborated by the improvement in the work record for 15 patients who were able to work full time without limitations, in contrast to only 3 patients preoperatively. They were further confirmed by the corresponding changes in symptoms in relation to the standard work load of the exercise-tolerance test, together with increased endurance, slower heart rate, higher systolic blood pressures during exercise and higher physical-fitness-index scores.

Nevertheless, a few patients, despite an improvement in attitude, continued to have specific job limitations, required easier jobs and were physically unable to participate in fairly sedentary recreational activities because of diminished cardiac reserve. Possibly, these patients have chiefly myocardial insufficiency, which may be manifested by heart failure,[4] in part due to carditis,[6] or the postcommissurotomy syndrome[2] often associated with rheumatic heart disease. Further studies by Harvey et al.[7] have differentiated some of these patients from those with chiefly a mechanical block at the mitral valve. These factors may account for the apparently poor correlation observed between functional results and the type and degree of valvulotomy obtained at operation.[8] In addition, they may provide an important basis for understanding the similarity of improvement in exercise tolerance between patients operated on and not operated on who have survived for a year or more and have been followed in this laboratory.[3] In this connection, the mean physical-fitness index increased from 9.3 to 12.0 in the former, and from 9.4 to 12.1 in the latter group of patients reported here. Whereas reasonably clear-cut examples of either myocardial insufficiency or mechanical block at the mitral valve undoubtedly occur, it has been our experience that most patients do not readily fall into either of these groups. Thus, it is likely that difficulties in evaluation will persist because of the presence of both mechanical block and myocardial insufficiency.

Meanwhile, surveys based on information obtained by questionnaires and similar information may not be entirely reliable when not controlled. Thus, Ellis and Harken[9] admit that "objective changes following mitral valvuloplasty are usually not striking." Yet the findings on personal examination are said to agree closely with results of questionnaires that indicated significant improvement in 77 per cent of 442 surviving patients.

It is obvious that the ultimate appraisal of this type of therapy must await the passage of time. Only then, when all patients — those operated on and those not operated on — are followed to death, will it be possible to determine whether the natural history of the disease and the longevity have been significantly altered.

Summary and Conclusions

Questionnaires designed to probe attitudes and salient facts of the medical record were sent to all surviving patients who had had mitral-valve surgery. Thirty-one (60 per cent), who were willing to return again for re-evaluation at an average of twenty-one months after operation, form the basis of this report. In addition to a careful history, review of the work and recreational records, physical and laboratory examinations, these patients were re-evaluated for standard exercise tolerance.

The results obtained are compared with the final preoperative evaluation that followed a period of intensive medical treatment. The discrepancies in evaluation by such diverse criteria as attitudes about illness, physical limitations, need for restrictions and continued medical therapy are discussed in relation to some of the changes observed in patients not operated on.

Attitudes toward heart disease and disability are greatly improved after mitral-valve surgery. There is only partial improvement in the findings on clinical examination and in the patient's ability to meet the requirements of daily life. Objective laboratory evaluation in terms of responses to standard exercise shows only moderate improvement, which, in fact, hardly exceeds that observed in some patients not operated on.

On the basis of observations in this laboratory, discrepancies apparent in the clinical evaluation of mitral-valve surgery may arise from failure to differentiate subjective attitudes from objective findings, to provide quantitative measurements of functional capacity before and after the operation, and to realize that surgical therapy is only incidental to one facet of rheumatic heart disease.

The final appraisal of mitral commissurotomy must await the objective demonstration of significant differences in functional capacity and longevity after operation.

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MOLAR SODIUM LACTATE*

Its Effect in Complete Atrioventricular Heart Block and Cardiac Arrest Occurring during Stokes–Adams Seizures and in the Terminal State

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IN previous communications we have discussed the action of molar sodium lactate in increasing the heart rate in patients with sinus bradycardia, partial and complete atrioventricular heart block and Stokes–Adams seizures, and have described the effects in the presence of terminal cardiac arrest.[1,2] The purpose of this presentation is to amplify the original observations and to report the experience gained from subsequent studies.

Methods and Materials

Molar sodium lactate¶ was administered to the following groups of patients:

To relatively asymptomatic patients with complete atrioventricular heart block whose rates varied from 32 to 71 per minute. The purpose was to determine its effect on the ventricular rate, the configuration of the ventricular complexes and to evaluate other toxic effects. The dosage ranged from 120 to 150 cc. given in ten to fifteen minutes. Electrolytes, blood chemical constituents and pH were determined before and after the infusion of the solution. In 1 patient, in whom molar sodium lactate given intravenously increased the ventricular rate, the substance was administered by mouth in a dose of 90 cc. four times daily over a period of four days to determine the effectiveness of the oral route, and particularly to ascertain its value in long-range therapy. In a second patient, it was administered for ten days in an attempt to prevent repeated Stokes–Adams seizures. These patients (except those on oral therapy) were followed for a period of one to one and a half hours from the beginning of the infusion.

To 3 patients with complete atrioventricular heart block who experienced Stokes–Adams seizures. The dose ranged from 40 to 80 cc. given intravenously by syringe in a period of one or two minutes.

To 12 additional patients with terminal cardiac arrest, 5 of whom were observed after intravenous infusion and 8 of whom were treated by intracardiac injection. Three of these patients were given the solution just before the episode of cardiac arrest; in the remainder, the solution was administered two to five minutes after the arrest had occurred.

Results

For simplification and conciseness, we shall present the results by illustrating each observation with a typical case report.

Effect on Heart Rate in Complete Heart Block

After the administration of 120 cc. of molar lactate in ten to fifteen minutes, the heart rate increased ap-

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¶Kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

preciably in 10 of 12 cases. In 4, the ventricular rate increased from 71 to 107, 40 to 50, 42 to 47 and 32 to 45 per minute, respectively. The atrial rate was comparably increased in most cases. In 3 cases with hyperpotassemia, the ventricular rate increased from

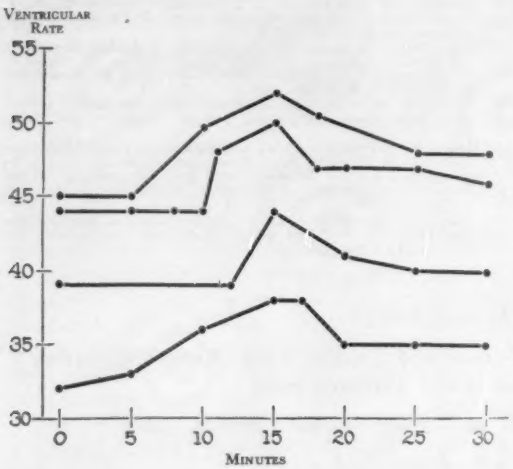

Figure 1. *Effect of 100 to 150 cc. of Molar Sodium Lactate on the Ventricular Rates of 4 Patients with Asymptomatic Complete Atrioventricular Heart Block.*

15 to 100, 28 to 71 and 30 to 52 per minute, respectively. In 2 cases, administration of molar sodium lactate in this dosage had no effect on the heart rate. In 1 of these, a patient with diabetes, the lactic acid level remained elevated over one and a half hours (the period of observation) suggesting lack of, or impairment in, utilization of the lactate. The typical effects on the ventricular rates in 4 cases are shown in Figure 1.

Production of Transient Ventricular Extrasystoles (Toxic Effects)

Case 1. F.S., an 87-year-old man, was admitted to the Philadelphia General Hospital on March 3, 1955, with a diagnosis of arteriosclerotic heart disease, aortic stenosis and cardiac enlargement. An electrocardiogram showed a slow ventricular rate (44 per minute) due to complete atrioventricular heart block and atrial fibrillation. On the next day, 100 cc. of molar sodium lactate was given intravenously over a period of 10 minutes. The control rate at this time was 39 per minute. The ventricular rate increased to 48 per minute within 10 minutes of the beginning of the infusion. This rise occurred at the time of the maximum increase in pH (from 7.45 to 7.50). Coincident with the maximum increase in rate, occasional extrasystoles, some of which were coupled, developed. The episode lasted approximately ½ minute. In about 1 hour, the rate had again decreased to 42 per minute (Fig. 2).

Sodium lactate resulted in an increase in the ventricular rate of approximately 20 per cent and produced transient ventricular extrasystoles, with coupling and slight alterations in the ST segment. Extrasystoles have been observed as a transient event in only 4 out of a total of 46 cases studied to date. Their duration was brief, lasting for several cycles, or at most, two minutes. They were particularly apt to occur at the height of the lactate effect in the older patients and in those with advanced myocardial disease. In 2 additional cases (studied subsequently), in which single or coupled extrasystoles were present in the control tracing, they became more numerous and were observed in pairs after lactate administration. However, most of our patients with advanced myocardial involvement failed to show extrasystoles in spite of the large doses of molar sodium lactate administered.

Alterations in QRS Complexes, T Waves and ST Segments

Case 2. C.L., a 70-year-old man, was admitted to the Philadelphia General Hospital on February 8, 1955, because of exertional dyspnea, orthopnea, pedal edema and chest pain. Examination showed the heart to be enlarged, the maximal impulse extending to the left, and a Grade 2 systolic murmur was heard over the entire precordium, loudest at the apex. The heart rate was regular at 40 per minute. The liver was enlarged, and its edge was felt 2 fingerbreadths below the right costal margin; ++ pedal edema was present. An electrocardiogram revealed a ventricular rate of 40 per minute due to complete atrioventricular heart block and atrial fibrillation. The diagnosis was arteriosclerotic heart disease, with cardiac enlargement and mitral insufficiency.

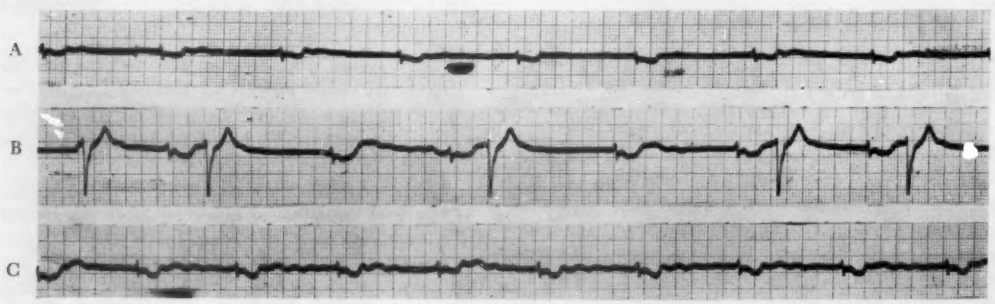

Figure 2. *Electrocardiograms (Lead 2) in Case 1.*

A *shows the presence of atrial fibrillation, with probably complete atrioventricular heart block. The ventricular rate is regular at 40 per minute.*

B, *tracing taken two minutes after the administration of 100 cc. of molar sodium lactate in ten minutes, shows the presence of a transient coupled rhythm that lasted about two minutes.*

C, *tracing taken twelve minutes after the end of the infusion, shows the increase in ventricular rate to about 48 per minute.*

The molar sodium lactate increased the idioventricular rate from 44 to 53 per minute, transiently narrowed the QRS complexes and produced inverted T waves and prolonged QT segments (Fig. 3).

The narrowing of the QRS complexes, which was observed in 8 of the 46 cases,[3] may have been the result of initiation of a higher pacemaker, increased conduction or improved nutrition (or both) of the heart muscle, or a change in the sodium potassium ratio in the extracellular fluid, producing a more favorable environment for normal ventricular depolarization.

The QT prolongation is similar to that observed with metabolic alkalosis.[4] After the administration of molar sodium lactate, we have observed these changes as a transient phenomenon lasting for five or six beats up to one or two minutes. The alteration of the T waves is, to some extent, secondary to narrowing of the QRS complexes. It is of considerable interest that the QT segments were prolonged (Fig. 3*C*), with the upright T wave, and that this was maintained in the cycles marked "X" with inverted T waves. That these effects are transient is shown in the tracing taken two minutes later (Fig. 3*D*), in which the QT segments are significantly shortened.

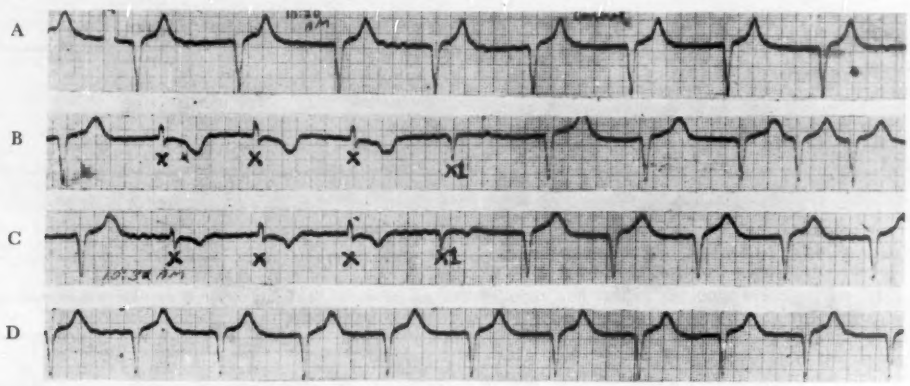

FIGURE 3. *Electrocardiograms (Lead 2) in Case 2.*

A, *control tracing, shows atrial fibrillation, with complete atrioventricular heart block (ventricular rate, 44 per minute, with almost regular rhythm).*

B, *tracing taken ten minutes after the beginning of lactate infusion (110 cc. of lactate given), shows the change in the configuration and narrowing of the QRS complexes, followed by inverted T waves and prolonged QT segments for three cycles; the QT segments are prolonged in this lead, even those with upright T waves.*

C, *tracing taken two minutes after the cessation of the infusion, shows an increase in the ventricular rate to 50 per minute. (Note also cycles [X] with narrowing of the QRS complexes, followed by inverted T waves and QT segments of normal length.)*

D, *tracing taken thirty minutes later, shows return to the control configuration of QRS complexes; the ventricular rate has increased to 53 per minute.*

Effect of Oral Administration

Although intravenous administration of molar sodium lactate appreciably increases the ventricular rate, the effect is quite transient. In certain cases of complete atrioventricular heart block, it would be of advantage if this increase could be sustained. The faster heart rate would be particularly helpful in the prevention of Stokes–Adams seizures and in increasing the cardiac output in patients in whom the slow rate is an important factor in the production of congestive heart failure owing to the extremely low and fixed cardiac output. The following case illustrates the effect when this solution is administered intravenously followed by continuous oral medication for a period of four days.

CASE 3. R.H., a 49-year-old woman, was admitted to the Graduate Hospital of the University of Pennsylvania on March 24, 1955, because of shortness of breath. The medical history revealed acute rheumatic fever at 5 years of age. In April, 1954, because of the development of progressive dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, ankle edema, episodes of dizziness and blurring of vision, she had been admitted to the hospital.

Physical examination showed a pale, dyspneic woman who appeared quite ill. The neck veins were moderately distended, and there was evidence of fluid at the bases of both lungs. The heart was enlarged, the maximal impulse extending to the left; a Grade 2 harsh, aortic systolic and a blowing, Grade 4 mitral systolic murmur were present. The liver edge was palpated 3 fingerbreadths beneath the right costal margin. There was 1 plus pretibial and ankle edema.

The pulse was 32, and the respirations 26. The blood pressure was 140/80.

On the day after admission, the patient was given 100 cc. of molar sodium lactate intravenously over a period of 15 minutes. A control electrocardiogram showed complete atrioventricular heart block, with atrial fibrillation and a ventricular rate of 32 per minute (Fig. 4*A*). The ventricular rate increased to 39 per minute at the end of the infusion.

Diuretics were administered every other day, without satisfactory results. Over a period of 6 days, while in the hospital, the patient gained 0.9 kg. (2 pounds) in weight in spite of a low-salt diet and mercurial diuretics. On March 31, molar sodium lactate* was started by mouth in a dose of 90 cc. 4 times daily. This was continued for 5 days; during the period of administration, the ventricular rate increased to a maximum of 52 per minute (Fig. 4). The rate generally ranged between 44 and 52 per minute during the hours of

*Supplied in a specially prepared syrup vehicle by Eli Lilly and Company, Indianapolis, Indiana.

lactate ingestion; however, during the night and before the 1st morning dose, the ventricular rate slowed to between 32 and 38 per minute. During these 5 days of lactate administration, coincident with acceleration of the heart rate, mercurial diuretics became effective, and the patient lost 1.3 kg. (3 pounds) of edema fluid. For the remaining 9 days of her hospital stay, the ventricular rate ranged between 48 and 60 per minute. She required fewer diuretics and lost an additional 1.8 kg. (4 pounds) of edema fluid. She was discharged on April 14, greatly improved.

Before discharge, a control electrocardiogram indicated a rate of 50 per minute. Immediately after exercise (10 sit-ups) the electrocardiogram showed no significant increase in the ventricular rate. After a rest period of about 30 minutes, another control electrocardiogram was taken (control ventricular rate of 50 per minute). Molar sodium lactate, 160 cc., was then given intravenously in 10 minutes; 15 minutes after the start of the infusion, the heart rate increased to 58 per minute.

The serum electrolytes, blood chemical values and pH recorded during the period of observation are presented in Table 1.

After maintenance on molar sodium lactate by mouth, as described above, an increase in the ventricular rate resulted, ranging from 50 to 55 per minute. This rate was maintained for a period of ten weeks. Still more significant, however, is the fact that the congestive phenomena improved along with the increase in heart rate (while the patient was kept on the same regimen as that employed with the slow heart rate). This improvement was probably the result of an increase in the cardiac output that accompanied the faster ventricular rate. This case is presented to suggest the possibility that the administration of molar sodium lactate by mouth has, in some cases at least, a salutory effect on maintaining or increasing the ventricular rate in a patient with complete atrioventricular heart block. The extent to which this result is accomplished and its frequency are currently being investigated.

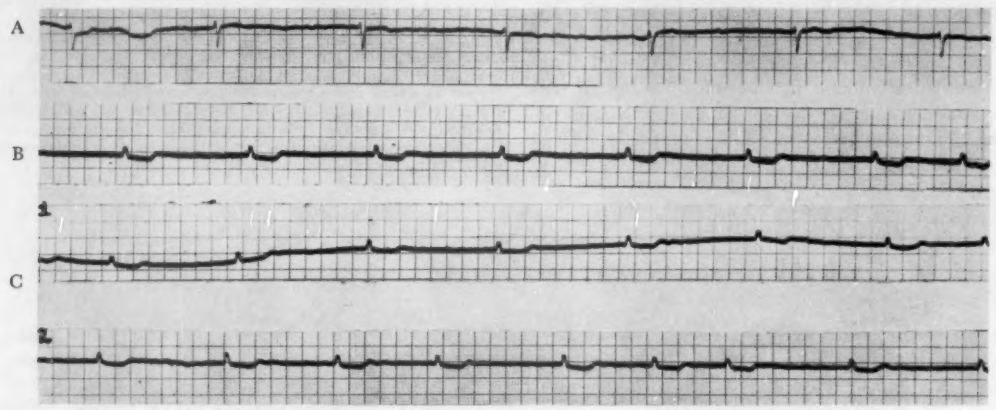

FIGURE 4. *Electrocardiograms in Case 3.*

A, control tracing (Lead 2), shows atrial fibrillation and complete atrioventricular heart block, with a ventricular rate of 32 per minute.

In B (Lead 1), tracing taken after the patient had received 360 cc. of molar sodium lactate a day by mouth within three days, the ventricular rate has increased to 40 per minute.

In C (Strip 1), taken in the morning of the fifth day before any lactate had been given by mouth, the ventricular rate has increased to 50 per minute.

TABLE 1. *Electrolyte and Other Data in Case 3.*

DATE	pH	SERUM SODIUM	SERUM POTASSIUM	CARBON DIOXIDE	CHLORIDE	VENTRICULAR RATE	REMARKS
1955		*milliequiv./liter*	*milliequiv./liter*	*vol. per cent*	*milliequiv./liter*		
Mar. 25		146	4.2	50	105	32	Control
Mar. 30	7.46	134	3.9		87	46	After oral lactate
Apr. 2:							
a.m.	7.42	137	3.8	74		38	Before daily dose
p.m.	7.44					50	After 2 doses
Apr. 5	7.43	143	4.1	69		44	No lactate
Apr. 12		140	5.5	59	103	48	No lactate

Effect on Hyperkalemia

Molar sodium lactate increases the ventricular rate, decreases QRS width and occasionally causes the restoration of a normal atrial rhythm in cases of hyperkalemia. The effect is immediate and striking. Our experience is based on a study of 4 cases, 1 of which is reported, as follows:

CASE 4. L.D., a 58-year-old Negro, was admitted to the Graduate Hospital of the University of Pennsylvania on January 4, 1955, because of a mass detected on x-ray study of the chest in another hospital. Because an exact diagnosis could not be made clinically, exploratory thoracotomy was performed on January 28, and a tumor that proved to be a benign mesothelioma was found and resected. On February 7 a fever resulting from an empyema developed; thoracentesis yielded about 400 cc. of sanguinopurulent fluid. The postoperative course was further complicated by upper gastrointestinal hemorrhage, apparently the result of activation of a peptic ulcer, and he was treated with transfusions of whole blood. An electrocardiogram taken on February 17 was suggestive of hyperpotassemia. On the next day the heart rate had decreased to 40 per minute. The elevated serum potassium (the value at this time was 7.8 milliequiv. per liter) was treated with glucose and insulin. By 9 a.m., on February 19 the heart rate was about 30 per minute (Fig. 5*A*—Strip 1), and the blood pressure, which had been 150/90 on admission, had dropped to 90/40. An electrocardiogram taken 20 minutes later revealed a ventricular rate of 28 per minute, with sinoatrial arrest, widening of the QRS complexes and episodes of paroxysmal ventricular fibrillation. Intravenous administration of molar sodium lactate was started immediately at a rate of about 150 to 200 drops a minute. Subsequently, a total of 740 cc. of molar sodium lactate was given by continuous intravenous drip at rates varying from 80 to 200 drops a minute over a period of 4 hours and forty minutes. The electrocardiogram was followed closely during this period, and blood for serial electrolyte studies was drawn (Table 2).

Within 8 minutes of the start of the sodium lactate administration the heart rate had increased from 18 to 38 per minute, and the blood pressure had risen from 90/40 to 130/70 (Fig. 5*C*). By 2 p.m., the serum potassium had decreased from 7.3 to 6.0 milliequiv. per liter, and the heart rate was 75 per minute. At the same time there was considerable clinical improvement. The blood pressure was 140/80. The sodium lactate was stopped, and 5 per cent glucose in distilled water was started. Two ampoules of 10 per cent calcium gluconate were given in the 1st of the 3 subsequent 1000-cc. infusions of 5 per cent glucose in water. The urinary output, which had been considered adequate (800 to 900 cc. per 24 hours) for the 2 preceding days, was scanty, and during the entire 23 hours and 25 minutes of observation, only about 150 cc. of urine was passed. By 10 p.m., on February 19 the patient appeared clinically able to withstand a thoracentesis, which was accordingly done. Periodic electrocardiograms up to midnight showed sustained improvement; the QRS complexes remained narrowed, the heart rate remained between 60 and 70 per minute, and the T waves in the precordial lead were much less peaked. He was not seen again until 8:40 a.m. on the following day, and no electrocardiograms were taken from midnight to 8:40 a.m. Although a nurse recorded the heart rate as 40 per minute at 4 a.m. no one was called to see the patient. At 8:40 a.m. the heart rate was about 30 per minute. He was cold and clammy. Before any therapy could be given, he suddenly went into collapse and ceased breathing at 8:45 a.m. An electrocardiogram showed ventricular fibrillation; 1 cc. of 1:1000 epinephrine was injected into the left ventricle, and manual respiration started, without any effect. No autopsy was performed.

The data in Table 2 illustrate the effect of the molar sodium lactate in increasing the heart rate, elevating the blood pressure, narrowing the QRS complexes and lowering the serum potassium. These effects coincided with an improvement in the patient's clinical state, and were maintained for a relatively long period (fourteen hours). However, because of the continued anuria, the cardiac manifestations of the hyperkalemia recurred. In 3 other cases under observation, the electrocardiographic and clinical manifestations of hyperkalemia were reversed by molar sodium lactate. Two of these subjects recovered.

Effect in Terminating Stokes–Adams Seizures

Molar sodium lactate solution was administered to 3 patients with Stokes–Adams seizures within a minute or less or an episode of cardiac standstill.* This infusion was efficacious in restoring cardiac rhythm on repeated occasions. In the first case in which this method was used, the heartbeat was restored on ten separate occasions within a period of two hours, after which cardiac rhythm was maintained without further sodium lactate administration for an additional two hours.[1] In 2 of the subsequent cases injections restored cardiac rhythm with ultimate recovery after numerous Stokes–Adams seizures. The doses employed ranged from 40 to 70 cc. given intravenously in about two minutes. The following case illustrates the use of molar sodium lactate in such a patient.

CASE 5. J.A., a 75-year-old woman, was admitted to another hospital on January 31, 1955, because of frequent Stokes–Adams seizures. The past history revealed that in June, 1954, the patient had an acute myocardial infarction followed by complete atrioventricular heart block and an occasional Stokes–Adams attack. She was hospitalized on December 27 of that year because of multiple Stokes–Adams episodes occurring over a period of several days. At this time, she was given epinephrine in oil, 2 mg., ephedrine, 25 mg. (⅜ gr.), and phenobarbital, 15 mg. (¼ gr.). The seizures were partially controlled by this regimen; however, because of congestive heart failure, she was digitalized before discharge from the hospital.

On January 29, 1955, she had another Stokes–Adams attack and, during the next 2 days before admission, experienced innumerable episodes. Digitalis was stopped on admission but the epinephrine in oil and the ephedrine were continued. Electrocardiographically, the attacks were of two types: ventricular asystole (cardiac standstill) and paroxysmal ventricular tachycardia and flutter. Pounding over the precordium was efficacious in restoring ventricular beating on multiple occasions. Between attacks the electrocardiogram showed a complete atrioventricular heart block with a rate of 33 per minute (Fig. 6); 40 to 80 cc. of molar sodium lactate was successfully used therapeutically by intravenous injection within 1 or 2 minutes on 40 separate occasions over a period of 10 days.

This infusion is effective in restoring cardiac beating after the cardiac arrest of Stokes–Adams attacks. During the seizure, the sodium lactate may be given by syringe or, in the presence of repeated episodes, by intravenous drip. Its continuous slow administration by the latter method may prevent further attacks, and if these should recur, the infusion rate may be speeded. In another patient with arteriosclerotic heart disease and numerous Stokes–Adams seizures occurring in association with complete atrioventricular heart block, intravenous administration of molar lactate restored ventricular rhythm. Because of the numerous Stokes–Adams seizures, lactate by mouth, in doses of 90 cc. four times a day, was given over a two-week period. During this time, there was a notable decrease in the number of attacks; however, slight pitting edema of the lower extremities developed. The patient died suddenly, and although the exact cause could not be determined, death was probably due to a Stokes–Adams seizure. Further experiments with the oral method of administration are being investigated.

*Since this paper was submitted for publication we have observed 4 additional patients in whom molar sodium lactate was efficacious in restoring cardiac beating.

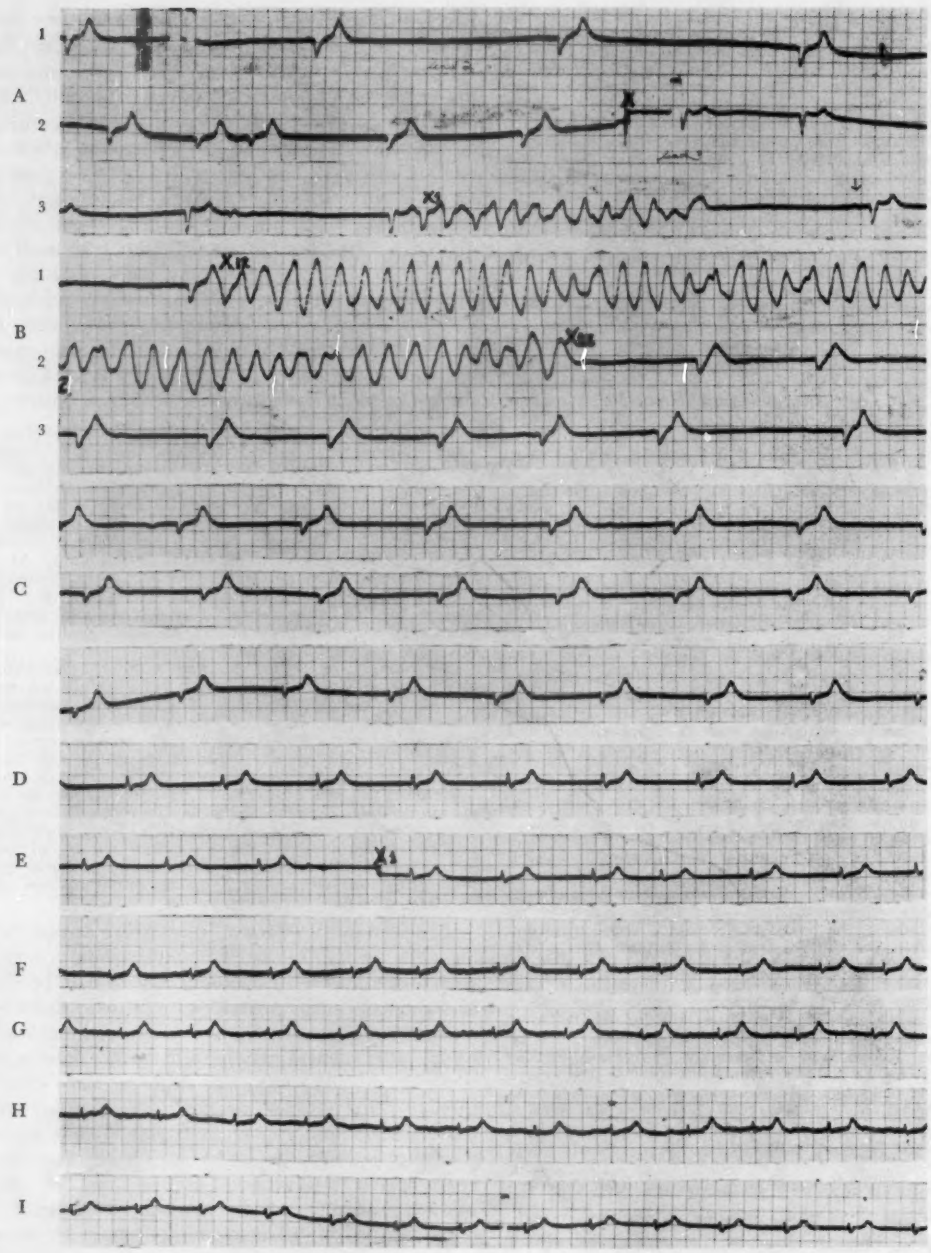

FIGURE 5. *Electrocardiograms in Case 4.*

A *shows strip 1, tracing taken at 9:10 a.m., indicating the slow idioventricular rate (18 per minute), with slightly widened QRS complexes followed by peaked T waves (Lead 2); strip 2, demonstrating irregularity in rhythm and rate; and strip 3, showing short paroxysm of ventricular flutter combined with fibrillation.*

B *shows strip 1, taken at 9:50 a.m., indicating paroxysm of ventricular flutter and fibrillation ending spontaneously. (Note the increased aberration of the QRS complexes, with continuation of a slow irregular rate; occasional P waves are seen.)*

C, *tracing taken eight minutes after* B, *shows a regular ventricular rate of 38 per minute, with decreased widening of the ventricular complexes; no P waves are observed.*

D = tracing (Lead 1), taken twenty minutes after B; *the ventricular rate is now 45 per minute.*

E, *tracing taken at 11 a.m. after 350 cc. of molar sodium lactate, shows a decrease in aberration of the ventricular complexes and decreased peaking of the T waves; the ventricular rate is now 47 per minute.*

F = *tracing taken at 12:20 p.m. after 600 cc. of molar sodium lactate; the ventricular rate is now 54 per minute.*

G = *tracing taken at 1:15 p.m.; the ventricular rate is 58 per minute.*

H = *tracing taken at 1:40 p.m.; the ventricular rate is 60 per minute.*

I = *tracing taken at 9:15 p.m. (twelve hours after sodium lactate was started); the ventricular rate is 63 per minute.*

Effect in Terminal Cardiac Arrest

Molar sodium lactate was used in 12 cases of terminal cardiac arrest — intravenously in 5 and by intracardiac injection in 7 (1 patient responded to intracardiac injection after the intravenous route had failed). Intravenous administration was usually begun two to four minutes after the heart had stopped.

In a few cases, the infusion was started after marked cardiac slowing but before complete arrest had occurred. The following cases illustrate the results obtained.

TABLE 2. *Serial Electrolyte Studies in Case 4.*

TIME	SODIUM	CHLORIDE	POTASSIUM	CARBON DIOXIDE	BLOOD UREA NITROGEN	REMARKS
	milliequiv./liter	*milliequiv./liter*	*milliequiv./liter*	*vol.per cent*	*mg.100/cc.*	
8:00 a.m.	129	102	7.3	37	90	Control
10:30 a.m.	131	101	7.1	47		1 hr. & 10 min. after lactate begun
1:00 p.m.			6.0			3 hr. & 40 min. after lactate begun
1:30 p.m.	145	98	6.2	65	42	4 hr. & 40 min. after infusion begun

CASE 6. A.N., a 36-year-old woman, was admitted to the Graduate Hospital of the University of Pennsylvania on April 18, 1955, in a semicomatose state with a diagnosis of probable brain tumor. The vital signs were normal until 2 days after admission, when, at 7:00 p.m., she suddenly stopped breathing and no pulse or blood pressure could be

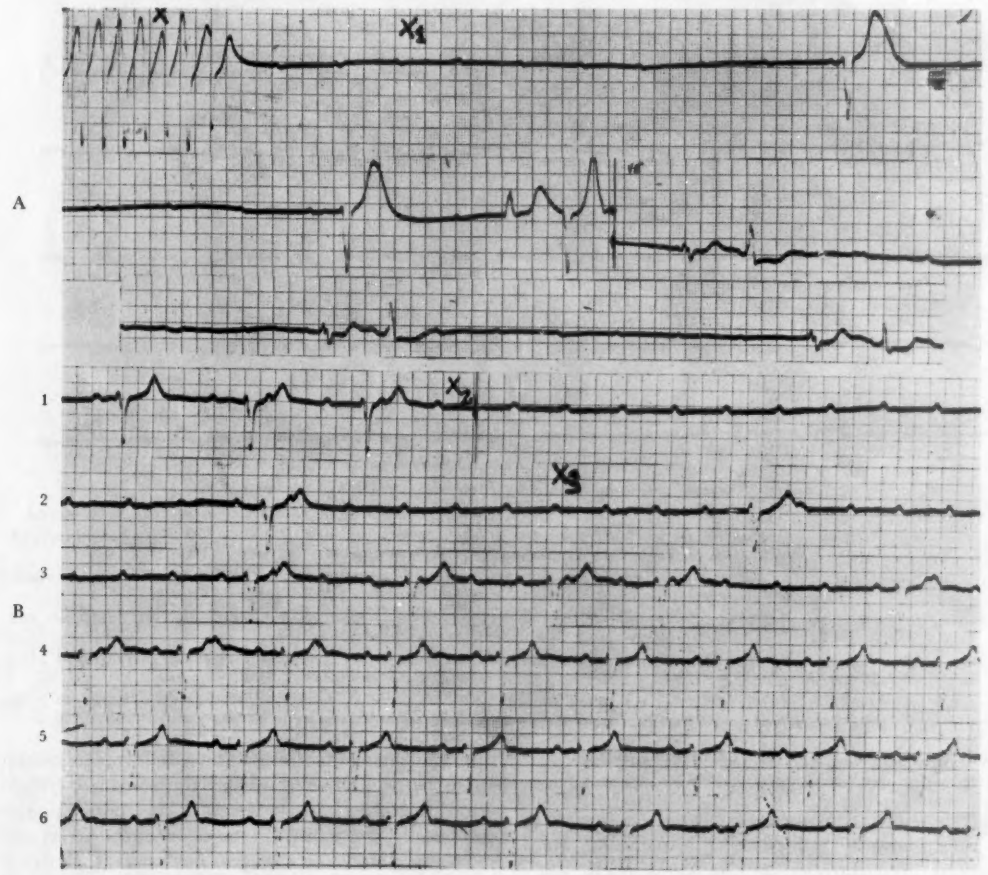

FIGURE 6. *Electrocardiograms in Case 5.*

A, *control tracing taken during a Stokes–Adams seizure, shows the rapid ventricular rate followed by an episode of cardiac standstill (upper strip). (Note the recurrence of idioventricular beats in the second strip.)*

B, *continuous tracing taken on another occasion (strips 1 - 6), shows the period of ventricular standstill at X_2 with maintenance of atrial rhythm. At X_3 sodium lactate was administered, with a gradual increase in the rate from 33 per minute in strip 1 to 38 per minute in strip 4, and abolition of the period of ventricular standstill. The atrial rate has also increased from 83 per minute to 100 per minute. In strips 5 and 6, the mechanism is changed to what appears to be partial atrioventricular heart block. This may be fortuitous with complete atrioventricular heart block and a 2:1 atrioventricular block, with the P wave buried in the T wave.*

obtained. She was immediately given artificial respiration (Neophor) and was taken to the operating room for emergency decompression of the brain. Several attempts to restore the blood pressure and pulse with Neo-Synephrine intravenously and by intracardiac injection were futile, and it was decided to give molar sodium lactate intravenously. One ampoule (40 cc.) was given in a period of 2 or 3 minutes, but the blood pressure and pulse continued unobtainable. Only after an additional 40 cc. had been given into the heart were strong pulsations in the neck detectable, and the heart sounds audible. The blood pressure was not recorded at any time. Five or 10 minutes after the molar sodium lactate had been given, an electrocardiographic machine became available, and the standard limb leads were taken. Arterial pulsations in the neck and heart sounds were easily detectable for about 7 or 8 hours after the administration of the sodium lactate. The patient failed to breathe by herself, however, at any time, and yet she was not cyanotic until the heart finally stopped beating at 4 a.m., on April 21. No additional sodium lactate was administered. Autopsy showed massive atelectasis and intracerebral hemorrhage secondary to a ruptured intracranial arterial aneurysm.

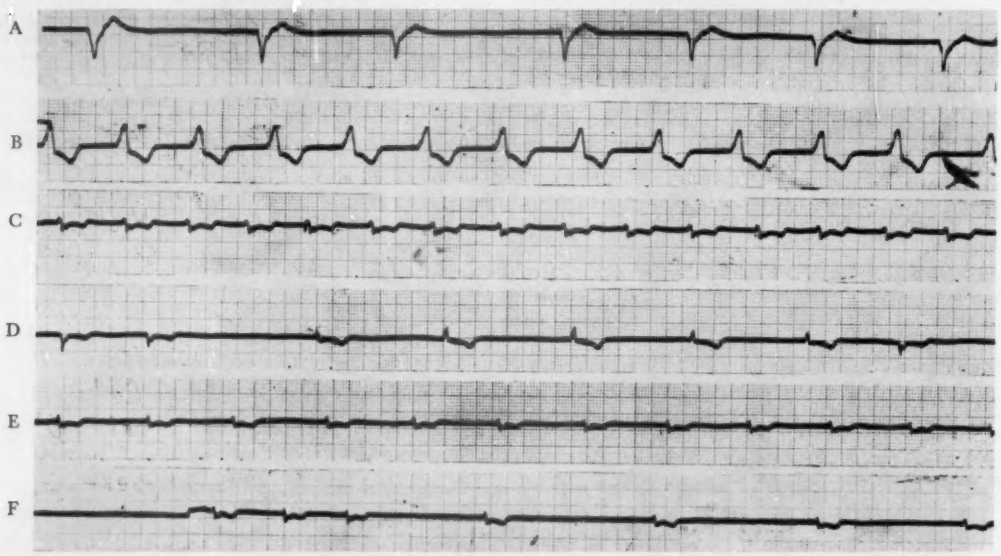

FIGURE 7. *Electrocardiograms in Case 7.*

A, control tracing, shows a ventricular rate of 35 per minute, with widened QRS complexes measuring 0.14 second.

In B, tracing taken within a minute of the start of molar sodium lactate intravenously at 150 to 200 drops per minute, the ventricular rate has increased to 63 per minute.

In C, tracing taken after 500 cc. of molar sodium lactate in approximately five minutes, the QRS complexes have decreased in width to 0.08 second, and the ventricular rate has increased to 75 per minute.

In D, tracing taken four minutes after C, with slowing of the lactate, there is slowing of the ventricular rate to 40 per minute; the QRS complexes remain narrow.

In E, tracing taken four minutes after D, with speeding of the lactate infusion, the ventricular rate has increased to about 60 per minute; there is still further narrowing of the QRS complexes to 0.06 second.

In F, tracing taken two minutes after E, when a total of 300 cc. of molar sodium lactate had been given intravenously, the rate has slowed to 35 per minute; final cardiac standstill occurred shortly afterward.

This case is of interest because cardiac beating and blood pressure were restored after intracardiac and intravenous administration of Neo-Synephrine had failed and because cardiac beating persisted for nine hours following treatment with molar sodium lactate.

It is difficult to determine definitely the period that had elapsed between actual cardiac arrest and the restoration of the heartbeat since the patient was not connected to an electrocardiograph, but presumably the interval was several minutes. Nevertheless, the electrocardiogram recorded five minutes after the intracardiac injection showed a sinus tachycardia and ST-segment depression but was otherwise relatively normal.

In the presence of terminal cardiac arrest, molar sodium lactate has had the following effects: the heart rate increased from 40 to about 100 per minute; bizarre QRS complexes became less abnormal, and the increased QRS width occasionally returned to normal; and with continuous artificial respiration, cardiac rhythm could be maintained for relatively long periods (however, the blood pressure could not be restored). As with other types of medication, it is important for cardiac resuscitation that molar sodium lactate be administered within the so-called critical period after the cardiac arrest. This period varies considerably, depending on the cause of the arrest and the related pathologic changes. Generally, the critical period is about one or two minutes after cardiac arrest.

CASE 7. M.C., a 45-year-old woman, was admitted to Philadelphia General Hospital on March 11, 1955, having been found comatose in her home. She was known to have rheumatic heart disease and atrial fibrillation and had been receiving 0.1 mg. of digitoxin daily and 0.12 gm. (2 gr.) of quinidine sulfate 3 times daily. Physical examination revealed

a well developed, well nourished, comatose woman. The apical heart rate was 84 per minute and irregular, and the temperature was 100.2°F. by rectum; the blood pressure was 160/110. There was dullness to percussion over the right lower lobe posteriorly, with subcrepitant rales heard in this area. Cardiac size could not be determined accurately by percussion. A loud mitral 1st sound and a short low-pitched mid-diastolic murmur were heard at the apex preceded by an opening snap. The patient had right-sided facial weakness and a flaccid hemiplegia on the right. She was treated with intravenous infusions of fluids, digitoxin and penicillin. On March 16 the temperature rose to 104°F. by rectum. On March 21 periods of ventricular asystole began to develop. An electrocardiogram at that time revealed widened, bizarre QRS complexes, with the ventricular rate averaging 30 to 40 per minute (Fig. 7), right-axis deviation, hypertrophy of the right ventricle and atrial fibrillation. At 12:15 p.m., molar sodium lactate was started at the rate of 80 drops per minute. After 50 cc. had been administered, the ventricular rate increased from 35 to 75 per minute, and the widened QRS complexes were narrowed (Fig. 7*C*). Despite continuous infusion, the patient again went into asystole and was pronounced dead at 12:30 p.m.

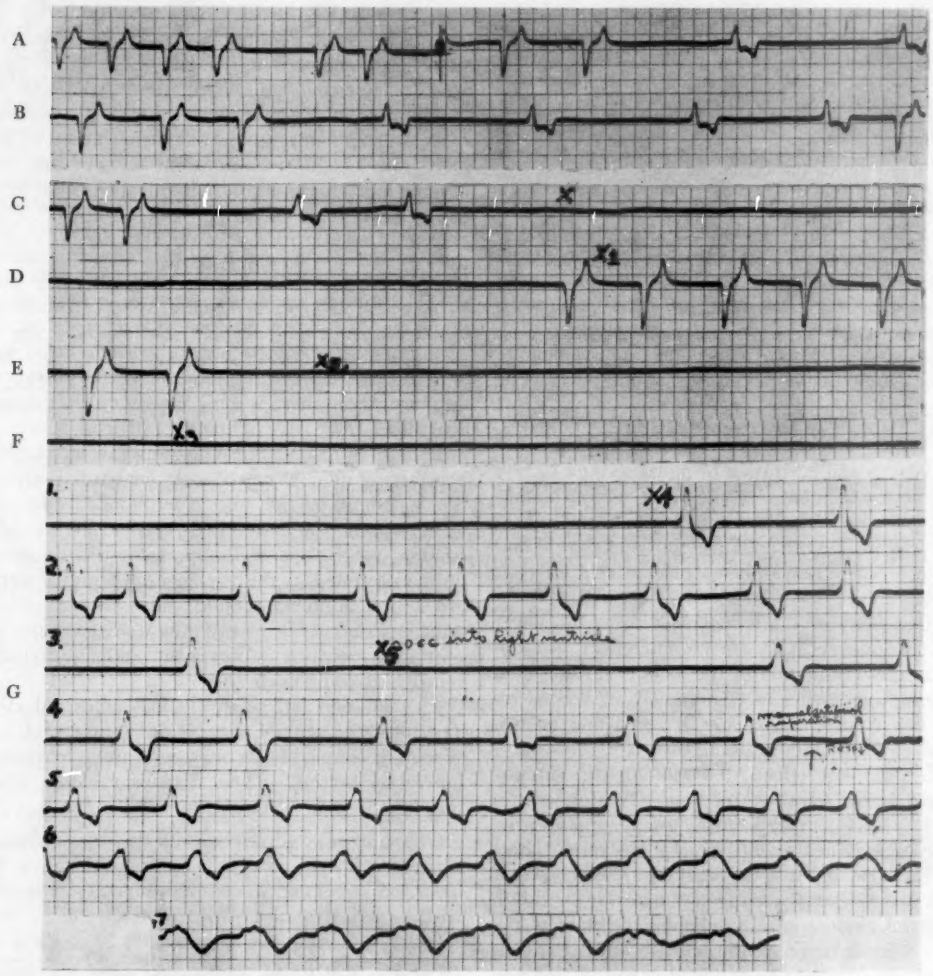

FIGURE 8. *Electrocardiograms in Case 8, a Patient with Carcinomatosis.*

A and B show slowing of the ventricular rate and aberration of the QRS complexes just before cardiac arrest.

At X in C, note the long period of cardiac standstill. This was followed by a spontaneous resumption of idioventricular beats (X_1) at a rate of about 55 per minute (strips D and E).

In F, at X_3, 20 cc. of molar sodium lactate has been injected slowly into the left ventricle.

G, taken thirty seconds after F, shows, at X_4 (strip 1), the restoration of idioventricular beating, which continues through strip 2. At X_5, during another episode of cardiac standstill, a second injection of 20 cc. of molar sodium lactate has been given into the right ventricle. This is again followed by restoration of idioventricular beating with increasing aberration of the QRS complexes; ventricular fibrillation occurred soon after strip 7.

CASE 8. S.S., a 59-year-old Negro, who was known to have adenocarcinoma of the stomach with hepatosplenomegaly and anemia, was admitted to the Graduate Hospital of the University of Pennsylvania on January 26, 1955, because of cramping abdominal pain, abdominal distention, weakness and marked anorexia. There was no history of dyspnea on exertion, palpitation or chest pain; there was + pretibial and ankle edema. He was pale and cachectic. The lungs were clear; the heart was at the upper limits of normal in

size, and no murmurs were audible. A regular rhythm was present. The blood pressure was 110/70, and the pulse rate 88 per minute.

The course in the hospital was rapidly downhill. On February 12, at 8 a.m., acute pulmonary edema and circulatory collapse developed. Cedilanid, 0.8 mg., was given intravenously, with oxygen and aminophylline, 0.95 gm. (3¾ gr.) intravenously, and the lungs partially cleared. At 10:35 p.m. the heart beat and respirations ceased. An attempt to give molar sodium lactate intravenously was unsuccessful, and after the electrocardiogram continued to show long periods of cardiac standstill, 20 cc. was injected into the left ventricle. This was followed by the restoration of ventricular rhythm (Fig. 8*C*). A 2d injection of 20 cc. of molar lactate into the right ventricle terminated in cardiac standstill after several minutes of sustained ventricular rhythm. Manual artificial respiration was given for only about 1 minute during the attempt at resuscitation.

This case illustrates the temporary restoration of cardiac beating with progressive increase in the heart rate after intracardiac injection of the molar lactate and marked narrowing of the QRS complexes. No further improvement was observed in spite of additional sodium lactate, and even with the electrocardiographic improvement, there was no improvement in the clinical state of the patient.

Discussion

Intravenous administration of molar sodium lactate was efficacious in increasing the heart rate in asymptomatic patients with slow ventricular rates due to sinus bradycardia, slow nodal rhythm and partial and complete atrioventricular heart block. This effect is apparently the result of an increase in cardiac rhythmicity that involves the higher as well as the lower cardiac pacemakers. The maximum effect was observed at the termination of the lactate infusion (ten to fifteen minutes after its beginning), or soon thereafter. The control rate tends to recur one or two hours after the lactate infusion.

Because of these effects, the solution was successfully used in the treatment of Stokes–Adams seizures (3 cases). Notable improvement was obtained in the therapy of 4 patients with hyperpotassemia. These effects included increase in heart rate, narrowing of the QRS complexes, lowering of the serum potassium and general clinical improvement in the state of the patient. The duration of the positive effect parallels the duration of alteration of blood chemical findings, electrolytes, pH and lactic acid concentration.

The mechanism of the lactate effect has not been definitely determined. The increase in cardiac rhythmicity was thought to be due to the alkalosis[5-8] and probably also the lactate radical. There is relatively little evidence that these actions are mediated via sympathetic or parasympathomimetic effects or both.[9]

Molar lactate was given by mouth in selected cases to increase the duration of the effects reported. Specifically, the object in 1 patient was to produce a sustained increase in and thereby to improve a previously refractory case of congestive heart failure. In another patient, there was a significant decrease in the number of Stokes–Adams attacks, but signs of congestive heart failure appeared. The effect of the oral method of administration is at present being further investigated.

Although the doses given intravenously ranged from 100 to 200 cc. in seriously ill patients and as much as 960 cc. was given, toxic effects were limited to premature ventricular contractions, whose duration, even when they occurred as coupled beats, was, at the most, thirty seconds to two minutes.

Failure to increase the ventricular rate in occasional cases of complete and partial atrioventricular heart block may be due to insufficient dosage; irreversible organic damage; and failure to metabolize the lactate, as observed in 1 of our cases.

Summary

Molar sodium lactate was effective in conspicuously increasing the heart rate in 10 out of 12 cases of asymptomatic, complete atrioventricular heart block. Although this effect is quite transient after intravenous administration, there is some suggestion that repeated oral doses may have a more prolonged action.

Because of its effect in increasing cardiac rhythmicity, this solution has been used in cardiac arrest of Stokes–Adams seizures and in terminal cardiac arrest. In 3 patients who manifested repeated Stokes–Adams seizures, ventricular rhythm was consistently restored after injection. In the presence of terminal cardiac arrest, the administration of this solution within a critical period of one or two minutes restores the heart beat and frequently improves the configuration of the ventricular complexes.

This solution has relatively few untoward effects. The most frequent of these is development of extrasystoles or coupled beats or an increase in extrasystoles previously present. These disappear within a short time of cessation of the infusion.

We are indebted to Dr. George W. Deitz for the privilege of reporting Case 5.

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GASEOUS INFLATION OF THE GASTROINTESTINAL TRACT

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LARGE accumulations of gas in the gastrointestinal tract have long been recognized to have certain diagnostic implications. Various therapeutic methods have also been devised for the removal of this gas. And yet, as Bockus[1] pointed out in the 1950 Caldwell Lecture, radiologists do not generally report the presence or location of lesser gas shadows, nor do physicians seem to pay much attention to them when organic disease is not present.

Perhaps these failures stem from a general lack of understandng of the mechanisms by which gas accumulates in the gastrointestinal tract — or from a reluctance to assign sufficient clinical significance to such gas. Or perhaps there has been overemphasis of the statements made in many textbooks on radiology that gas appears radiographically in the adult small intestine only in the presence of organic disease.

Nevertheless, sufficient evidence has now accumulated to suggest that a common mechanism is involved in all cases of gaseous distention, whether or not the distention is confined to a short gastrointestinal segment and whether or not it is associated with organic disease. It is the purpose of this paper to review briefly this evidence, to re-emphasize the most important method by which gas reaches the gastrointestinal tract and to present 2 supporting cases.

It may be said that the accumulation of gas anywhere in the gastrointestinal tract represents the disparity at any given time between gas-forming and gas-removing mechanisms. Aside from the experimental inflation of the lumen by intubation, there are three possible means by which gas may reach the gastrointestinal tract: by ingestion; by diffusion from the blood stream; and by chemical change of intestinal contents. Aside from the artificial methods of removing it, there are three means by which gas may leave the gastrointestinal tract: by ejection — through mouth or anus; by diffusion into the blood stream; and by absorption through the intestinal wall.

CAUSES

The once prominent role of putrefaction as the source of gas has long since been reassigned to what is loosely called "air swallowing." It is now known, as the result of many analyses of intestinal gases,[2-5] fluoroscopic and radiographic observations[6,7] and animal and human experimentation,[8-12] that 70 per cent of the gas found in the gastrointestinal tract — even in cases of intestinal obstruction — results from the ingestion of air. Moreover, it has been shown that even the muscular act of swallowing is not necessary for the transport of air from the mouth to the stomach. Indeed, it appears that another mechanism of air ingestion, involving unconscious relaxation of the superior esophageal sphincter and the creation of negative pressure in the esophagus as the result of inspiration against a closed glottis, is capable of drawing 1000 to 2000 cc. of air into the esophagus within three to five minutes.[13] It has been shown further that nervous or uncomfortable patients may ingest by these methods up to three times as much air as normal, calm controls.[12] In addition, voluntary belching, which entails the conscious control and use of the superior esophageal sphincter mechanism, may actually introduce more air into the stomach during the initial phases of this act than may be eructated at its completion.[12] This ingested air, whether swallowed or aspirated, consciously or unconsciously, may appear at the cecum in six to fifteen minutes, and may be passed as flatus within thirty minutes.[7] And unless the mechanisms by which the gastrointestinal tract rids itself of gas keep pace, accumulations of this air may appear in any segment or may fill the tract entirely.

On the other hand, chemical change of intestinal contents, or putrefaction, contributes little, if any, to gaseous distention.[2,11,14] Even in cases of small-bowel obstruction, less than 10 per cent of the gas above the obstruction has been found to result from putrefaction.[2] Moreover, other factors, such as stasis and impairment of circulation to the intestine, are necessary before putrefaction achieves even this small degree of significance.

A somewhat more important source is the diffusion of various gases from the blood stream into the stomach or intestinal lumen. Gases in the stomach or intestine obey physical laws and thus tend to come into equilibrium with those in the blood. Although a number of observers have noted the excretion of gases from the blood into the stomach[4] and intestine,[14,15] they are generally agreed that this mechanism is responsible for less than 20 per cent of the gas found, even above a point of small-bowel obstruction.

It seems clear, therefore, that the ingestion of air by swallowing or by aspiration is the most important means by which gas reaches the gastrointestinal lumen. Despite the voluminous experimental evidence that this gas, once ingested, can progress through the pylorus and often to the anus, there are relatively few case reports in the literature demon-

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strating the complete filling of the gastrointestinal tract with air, in the absence of organic disease. In 1930 Winkelstein[16] reported 4 such cases briefly. Ritvo[17] presented a roentgenogram demonstrating the entire gastrointestinal tract filled with gas, without, however, including a case history. Maddock, Bell and Tremaine[12] described a similar case. Several other authors of textbooks on roentgenology[18,19] refer to inflation of the gastrointestinal tract with gas as the result of aerophagia, but none include specific case reports or illustrations.

Since each demonstration that the simple ingestion of air is capable of filling the entire gastrointestinal tract constitutes a further link in the chain of evidence supporting this mechanism of gaseous inflation, 2 such cases are reported below.

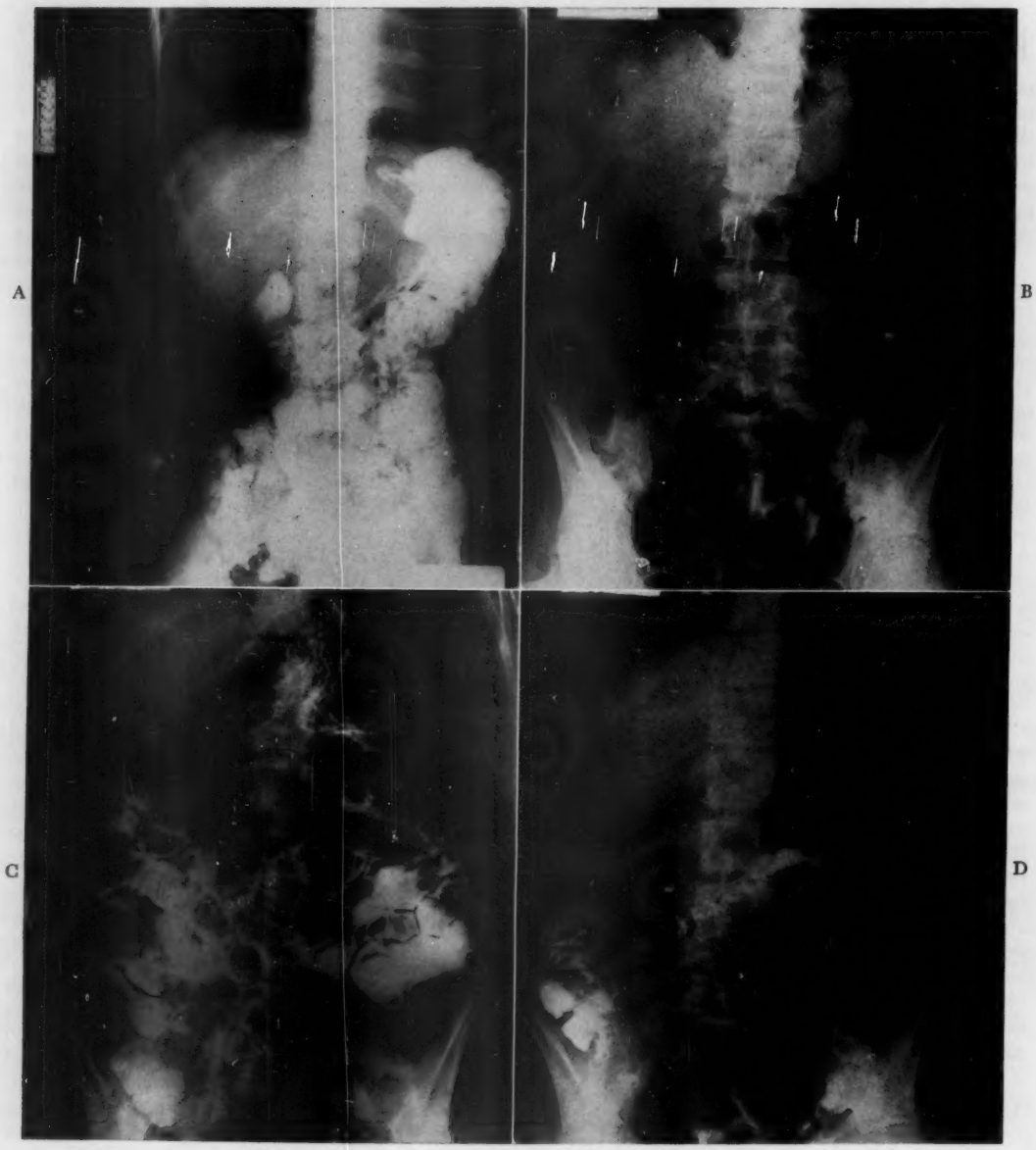

FIGURE 1. *Roentgenograms in Case 1.*

Gastrointestinal Series in 1952 (A) *gives no evidence of excessive gas in the gastrointestinal tract. A survey film of the abdomen* (B) *shows gas outlining the stomach, many loops of small intestine and the colon. A small-bowel study* (C), *showing barium mixed with gas throughout the undilated small bowel, gives no evidence of obstruction; gas is also noted outlining the stomach and the colon. An evacuation film after a barium enema* (D) *again shows the entire gastrointestinal tract outlined by gas.*

Case Reports

Case 1. J.P., a 35-year-old divorced woman, was first seen by us on February 25, 1955, complaining of gas and diarrhea of 2 years' duration.

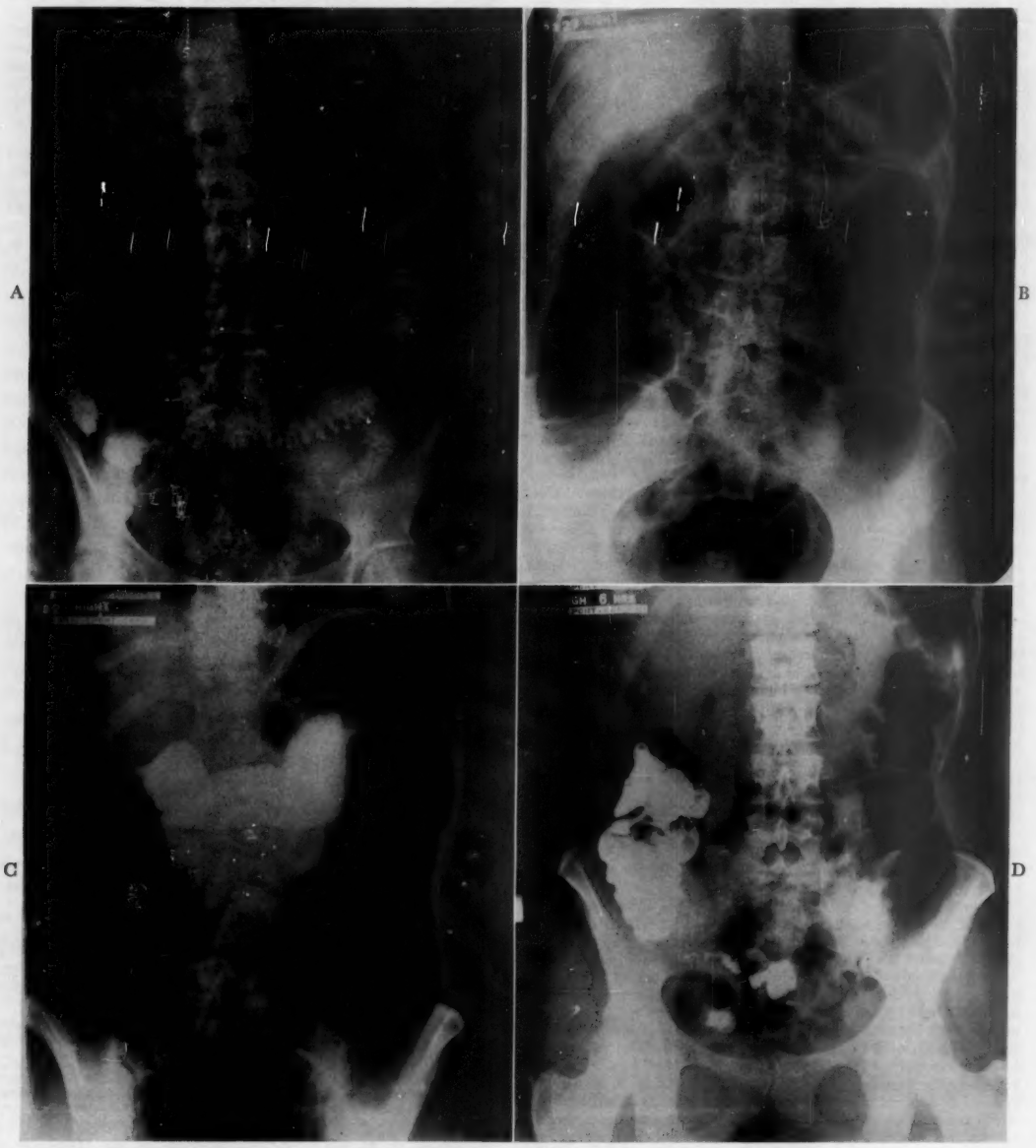

Figure 2. *Roentgenograms in Case 2.*

An evacuation film after a barium enema (A) *shows the huge magenblase and the gas in the loops of small bowel. A survey film of the abdomen* (B) *shows gas outlining the stomach, loops of small bowel and the colon. A gastrointestinal series* (C) *shows extensive collections of gas in the fundus of the stomach, in the loops of small bowel and throughout the colon. A six-hour gastrointestinal series* (D) *shows normal progress of the barium column and evacuation of all gas but that in the transverse and descending colon.*

She had first noted severe constipation, bloating, belching and excessive flatus after the repair of a right indirect inguinal hernia in 1949. She had then required enemas twice a month for relief. She also had suffered weakness and a weight loss of 20.4 kg. (45 pounds). In March, 1952, she had been admitted to the Grace-New Haven Community Hospital, where studies had revealed a severe hypokalemic, hypochloremic alkalosis that had finally been ascribed to self-induced vomiting. A gastrointestinal series had shown no gaseous inflation of the gastrointestinal tract (Fig. 1*A*). Subsequently, she regained the lost weight and felt well. However, in 1953, after her mother developed a severe psychosis, the patient again noted gas, bloating, belching and excessive flatus. In addition, she had regurgitation and heartburn. These symptoms were accompanied by 4 or 5

loose stools a day, each affording temporary relief from her distress. She also noticed sharp pain in the right costovertebral angle of the back, relieved by the passage of gas by mouth or by rectum, and by the passage of a bowel movement. There had been soreness over the whole right side of the abdomen. Some of the stools consisted entirely of mucus, but she had passed no blood. She had not been constipated. Her appetite was good despite the persistence of her symptoms, and there were no known food offenders. She denied conscious aerophagia. However, she could belch voluntarily, although some of her belching was involuntary. She had been divorced in November, 1954, and she admitted that she was tense and unhappy.

The family history, past history and a review of the systems were noncontributory.

Physical examination revealed a slim, well developed, well nourished woman in no acute distress, who weighed 51.7 kg. (114 pounds). She had a shy, formal and unbending manner. However, she expressed no unusual ideas or sentiments and was fully oriented and co-operative. The blood pressure was 114/74. The abdomen was soft, moderately distended and tympanitic in all quadrants, but without tenderness or rigidity. There was a scar of a right herniorrhaphy. There were no palpable organs or masses. The remainder of the examination was not remarkable.

Sigmoidoscopy showed a shallow fissure in the anal canal. The mucosa in the rectum was red and edematous. The sigmoid mucosa presented a similar appearance, and there was spasm throughout. The findings were typical of those seen in the syndrome of the irritable colon.

Blood counts revealed a mild secondary anemia. The remainder of the laboratory examination was within normal limits.

X-ray study of the chest showed no thoracic abnormalities, but there were large collections of gas in the stomach and in the splenic flexure of the colon. Fluoroscopy and a survey film of the abdomen indicated extensive gas in the stomach, small bowel and colon (Fig. 1*B*). The gas-filled loops were not arranged in a step-ladder pattern, however, and there was no evidence of fluid levels. A small-bowel series disclosed no intrinsic disease of the gastrointestinal tract (Fig. 1*C*). The air and barium mixture provided an excellent air-contrast study. The barium passed rapidly through the small bowel, presenting no evidence of obstruction. The loops appeared to be inflated to their full caliber, measuring 2.5 to 3 cm. in diameter, and were nowhere unduly dilated. A barium-enema examination revealed only spasm in the sigmoid colon, without evidence of organic defect (Fig. 1*D*).

The final diagnoses were psychoneurosis, irritable-colon syndrome, secondary anemia on a nutritional basis and severe air ingestion, secondary to the psychoneurosis.

CASE 2. R.P., a 34-year-old housewife, was admitted to the Bridgeport Hospital on April 27, 1953, with a chief complaint of abdominal distention of 6 and excessive belching of 4 months' duration.

She stated that since November, 1952, she had noted that her abdomen was swollen intermittently and felt as if it were full of gas. Occasionally, it became painfully "hard." The pain radiated to the area between her shoulder blades. There was also pain in the left lower quadrant. The stools had been "a little thin" but otherwise not remarkable. She had been eating everything, but "very often while eating I have to get up and belch." She often felt that she could not swallow her food because of the belching. There were no known food offenders and no known weight loss. Belching had been so annoying that she had been unable to stay in groups or to remain in a theatre or at church. She felt quite nervous and tired and slept poorly. Her attending physician added that when he had seen her 1 week before entry, she was "so distended that a thorough examination of the abdomen could not be done" and that it was therefore impossible to do a bimanual pelvic examination.

The family history, past history and review of the systems were noncontributory.

Physical examination revealed a well developed, moderately well nourished woman in no acute distress who weighed 51.8 kg. (115 pounds). The abdomen was slightly distended, but no organs or masses were palpable. The remainder of the physical examination revealed no abnormalities.

The pulse was 86, and the blood pressure was 120/68.

Laboratory examinations were within normal limits.

Barium-enema study showed a hypotonic colon, but was otherwise not remarkable. The evacuation film indicated considerable gaseous distention of the stomach and small intestine (Fig. 2*A*). At fluoroscopy before the gastrointestinal series, extensive air collections in the abdomen were noted. A survey film showed extensive gas throughout the stomach, small bowel and large bowel, without evidence of obstruction (Fig. 2*B*). The gastrointestinal series revealed a small sliding type of hiatus hernia and again demonstrated extensive filling of the entire gastrointestinal tract with air swallowed during fluoroscopic observations (Fig. 2*C*). The 6-hour film disclosed normal progression of the barium (Fig. 2*D*), and it was noted that the bowel had emptied itself of much of the gas by the end of the examination.

While in the hospital, the patient appeared more relaxed and suffered less belching and distention. She was much relieved by an explanation of the cause of her symptomatology and was discharged from the hospital considerably improved.

The final diagnoses were anxiety hysteria, hiatus hernia of the small, sliding type and severe air ingestion, secondary to the hysteria.

SUMMARY AND CONCLUSIONS

Experimental and clinical evidence indicates that the ingestion of air, by swallowing or by aspiration, is the most important method by which gas reaches the gastrointestinal tract.

A perusal of the literature reveals only 6 reported cases of filling of the gastrointestinal tract with gas in the absence of significant organic disease.

Two cases are presented as further evidence that ingestion of air is the main source of gaseous inflation of the gastrointestinal tract.

We are indebted to Dr. Frank Northman for permission to include his records in the report of Case 2 and to Dr. Joseph Esposito, senior attending radiologist, Bridgeport Hospital, for permission to reproduce the roentgenograms in Case 2.

114 State Street

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RECURRENT INTUSSUSCEPTION ASSOCIATED WITH HYPERTROPHY OF PEYER'S PATCHES*

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INTUSSUSCEPTION is considered by most clinicians to be one of the most important acute abdominal conditions occurring in infancy and childhood. This is attested to by the voluminous literature that has appeared on the subject in recent years. Numerous reports citing series of hundreds of cases are in general agreement that the etiology of intussusception in the younger age groups is for the most part not understood. The mechanism whereby the terminal ileum telescopes into the colon and becomes incarcerated remains an enigma. What is equally puzzling is why this condition, having been relieved by one form of therapy or another, does not recur more often. It is generally agreed that, aside from simple manual reduction of the intussusception, the surgeon is ill advised if he attempts any special operative procedure designed to prevent recurrence. Gross[1] reports a recurrence rate of only 2 per cent in a series of 702 cases, stating "the largest number of recurrences ever reported in one individual was in a child who required four operations." It is our purpose to describe the clinical and pathological findings in a child who underwent five surgical reductions of a recurrent ileocolic intussusception followed by ileocecal resection with complete recovery. It is hoped that the pathological studies in this unusual case may shed some light on the problem of recurrent intussusception with particular reference to its etiology and management in infancy and childhood.

CASE REPORT

A 4-month-old male infant was first admitted to Syracuse Memorial Hospital on January 28, 1951, because of vomiting and the recent passage of melena associated with mucus in the stool. He had apparently experienced no abdominal pain. Physical examination revealed a well developed and well nourished infant weighing 7 kg. (15 pounds, 8 ounces). The vital signs were normal. Complete physical examination, including abdominal palpation, and routine laboratory tests were negative. Barium-enema study showed a filling defect in the colon just proximal to the hepatic flexure, characteristic of intussusception. Operative reduction was carried out by Dr. Lawrence Pickett 6 hours after admission. No intrinsic abnormality of the terminal ileum, which had intussuscepted into the colon, was discerned by Dr. Pickett. The post-operative course was uneventful.

Readmission to the hospital was necessary on April 9, when the patient was 7 months old, because of constipation, abdominal cramps and the presence of flecks of bright-red blood in the stool returned after an enema. Physical examination disclosed a mass in the right subcostal region. The laboratory data were noncontributory. Barium-enema study showed a filling defect in the hepatic flexure characteristic of intussusception that could not be reduced by the usual hydrostatic pressure employed in the introduction of barium. Exploration by one of us (E. L. S.) revealed ileocolic intussusception, which was easily reduced. The terminal ileum appeared edematous after the reduction. Incidental appendectomy was performed. The postoperative course was not remarkable. Pathological examination of the appendix disclosed no gross abnormality. The microscopical sections gave no evidence of intramural inflammatory changes. The mucosal lymphoid follicles were small, and the germinal centers were ill defined. The pathological report indicated that the appendix was normal.

The patient was readmitted to the hospital on August 9 at the age of 10½ months because of severe intermittent abdominal pain associated with vomiting. Physical examination revealed a mass in the right upper quadrant of the abdomen. Barium-enema study disclosed the same findings noted on previous admissions: an irreducible intussusception at the hepatic flexure. Surgical reduction of the ileocolic intussusception was performed, and biopsy of one of the many enlarged mesenteric lymph nodes was carried out. The postoperative course was marked by moderate fever, which subsided after a few days. Gross examination of the lymph node showed nothing unusual. Microscopical examination revealed the cortical lymphoid nodules to be normal in size, and few of them exhibited germinal-center activity. Slight reticulum-cell overgrowth was present. The pathological diagnosis was chronic hyperplastic lymphadenitis.

The patient, at 20 months of age, was admitted to the hospital for the 4th time on May 22, 1952, because of recurrent signs and symptoms of intussusception, which was again confirmed by barium-enema studies. The roentgenologist attempted unsuccessfully to reduce the intussusception by hydrostatic pressure. At laparotomy a diligent search was made for some intrinsic lesion of the ileum responsible for the recurrent ileocolic intussusception. Edema of the ileum in its terminal portion and enlarged mesenteric glands were the only abnormalities noted in association with the ileocecal intussusception. The patient recovered following operative intervention without sequelae. Barium-enema study several weeks later, when he was asymptomatic, showed no abnormality of the colon or terminal ileum although the ileum was not too clearly seen.

On December 10, 1952, at the age of 27 months the patient was admitted to the hospital for the 5th time a few hours after the onset of crampy recurrent abdominal pain. Once again barium-enema study disclosed an irreducible ileocolic intussusception in the region of the hepatic flexure. At operation the ileocolic intussusception was reduced by Dr. Daniel Burdick; no intrinsic abnormality of the ileum, except edema, could be found. A mild pyrexia marked the otherwise uneventful postoperative course. One month later small-bowel intubation was carried out in preparation for x-ray study of the small bowel. Unfortunately, the examination was not carried out owing to the patient's indisposition.

On March 9, 1953, at the age of 2½ years, the patient was admitted to the hospital for the 6th time because of abdominal cramps. He did not appear particularly ill. Barium-enema study disclosed a temporary obstruction at the hepatic flexure characteristic of intussusception that was reduced with pressure to the cecum, beyond which no further reduction could be accomplished.

At laparotomy on March 13, 1953, it was noted that the ileocolic intussusception had spontaneously reduced itself completely. The terminal ileum in its last few centimeters presented a definite thickening, which the operators assumed was residual edema of the pre-existent intussusception. The mesenteric glands were much enlarged. Ileocecal resection was carried out, intestinal continuity being restored by means of a side-to-side ileoascending colostomy. The patient was discharged from the hospital 2 weeks later.

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Gross examination of the resected specimen, including the ileum and cecum, revealed it to measure 18 cm. in length (Fig. 1). The mucosal surface of the 1st 6 cm. of ileum appeared normal except for a solitary, slightly raised, irregular patch, measuring 1.5 by 1 cm., located at the proximal line of resection. At a distance of 6.5 cm. from the proximal

FIGURE 1. *Terminal Ileum, Showing the Two Annular Thickenings with an Ulcerated Zone between Them. The proximal limit of the ileal resection is at the left border of the illustration.*

limit of resection there was an abrupt change in mucosal pattern produced by a thickening measuring 2.5 cm. in length and completely encircling the bowel lumen. The mucosal folds within this area were markedly thickened and wormlike in consistence. A similar area of mucosal alteration that began at a point 10 cm. from the proximal line of resection extended to involve the ileal surface of the ileocecal valve. This zone measured 3.3 cm. in length and also completely encircled the bowel lumen. Between these 2 zones the mucosa of the ileum revealed 4 shallow, ulcerated foci; the margins about the ulcerated areas were soft and slightly rolled. Many small, soft, tan lymph nodes were identified

FIGURE 2. *Microscopical Appearance of the Annular Thickening Nearest the Proximal Line of Resection (X 7). The hypertrophic germinal centers tend to flatten the mucosal epithelium and compress the submucosa.*

within the small-bowel mesentery and adjacent to the serosa of the cecum.

Microscopical examination of the specimen showed the mucosa in the involved areas to be thrown into broad, polypoid folds composed of enormous aggregates of mucosal lymphoid tissue (Fig. 2). These lymphoid masses were sharply circumscribed, with unusually marked germinal-center activity that narrowed the mature lymphocytes to a thin rim at the margins. The majority of the cells comprising the germinal centers were medium-sized lymphocytes with pale vesicular nuclei. Prominent nucleoli and mitotic activity were observed within many of these cells. Phagocytic reticular cells were present within the germinal centers in large numbers, and rare plasma cells were noted. These giant masses of lymphoid tissue compressed the overlying mucosa, producing a flattened appearance instead of the usual villiform pattern. In some areas the pressure atrophy had resulted in superficial mucosal ulceration (Fig. 3). Although mucosal in location, the lymphoid tissue compressed the muscularis mucosa and at times so narrowed the submucosa that it became impossible to identify this coat of the bowel. There was slight, diffuse scattering of lymphocytes within the submucosa, but this was never striking. The muscularis externa was considerably hypertrophied and was nearly equal in thickness to the edematous serosa in most areas. A normal Peyer patch from a 1-year-old child is

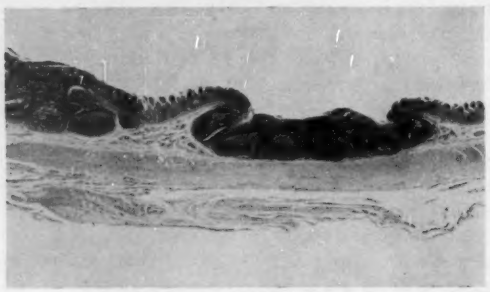

FIGURE 3. *Microscopical Appearance of an Area of Mucosal Ulceration between the Two Zones of Annular Thickening (X 7).*

shown in Figure 4 for comparison with the process described above. Microscopical examination of the enlarged mesenteric lymph nodes disclosed the cortical lymphoid nodules to be well defined and not unusually large (Fig. 5). Some germinal-center activity was present, but it was in no way comparable to the process within the ileum. The pathological diagnosis was giant-follicle hypertrophy of Peyer's patches.

When last seen, more than 2 years after the ileocecal resection, the patient, at 4 years of age, was completely asymptomatic. His weight and development were normal for his age. The mother reported that he had perfectly normal bowel habits and was free of abdominal complaints.

DISCUSSION

The cause of intussusception in children is usually unknown whereas in adults a definite mechanical fac-

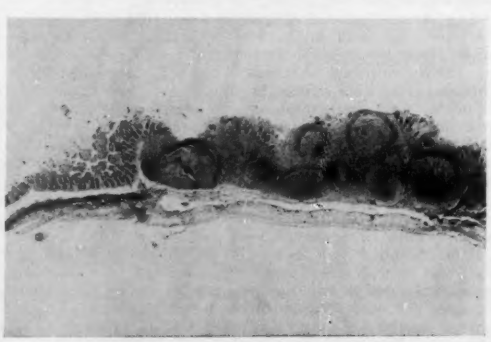

FIGURE 4. *Microscopical Appearance of a Normal Peyer Patch in a One-Year-Old Child (X 11).*

tor is usually quite apparent. Of 702 cases in children cited by Gross[1] only 43 (6 per cent) had a demonstrable cause. Of these 43, 32 were cases of Meckel's diverticulum, 5 were polyps, and 3 were duplica-

tions of the terminal ileum. No mention of lymphoid hyperplasia of Peyer's patches is made by Gross[1] in his textbook. Elsewhere, Gross[2] has described a prominent ileocecal valve or a mass of lymphoid tissue as an adequate cause for recurrent ileocecal intussusception, for which he recommends ileocecal resection. Perrin and Lindsay[3] surveyed a series of 400 cases in infants and children under two years of age, with almost exclusive involvement of the ileocecal region of the intestinal tract, the majority of which were caused

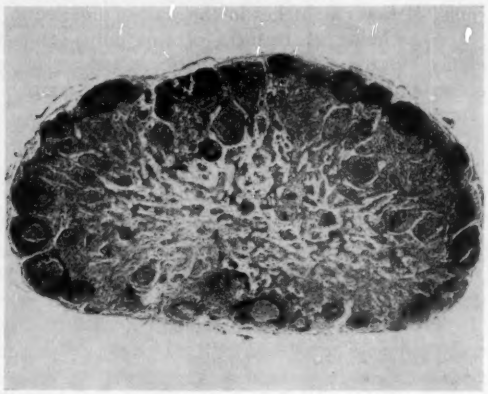

FIGURE 5. *Microscopical Section of an Enlarged Mesenteric Lymph Node, Showing Some Germinal-Center Activity with Dilated Medullary Sinuses and Prominent Reticular Cells (X 13).*

by inflammatory swelling of the lymph tissue in the terminal 15 cm. of ileum. Their anatomic studies revealed that during the first year of life this area of terminal ileum was studded with lymphoid tissue, which gradually disappeared as the child grew older. These authors were convinced that the age incidence of intussusception varied directly with the prominence of the lymphoid tissue in the terminal ileum, although they were at a loss to explain the precise cause of the inflammatory swelling of the lymphoid tissue.

Although this hypothesis of Perrin and Lindsay has not been generally accepted, isolated reports support their thesis. Dennis[4] described 2 children whose intussusception he attributed to polypoid hyperplasia of Peyer's patches in the terminal 2 cm. of ileum; both were treated by ileocecal resection, with recovery. O'Sullivan and Child[5] reported 2 similar cases treated by resection in which microscopical examination revealed hypertrophied submucosal lymphoid follicles. It should be pointed out that in both these cases, as well as in those cited by Dennis, laparotomy disclosed polypoid ileal masses, and resection was immediately carried out. In the case presented above, 3 different surgeons were unable to delineate any mass in the edematous ileum on repeated surgical explorations. This accounted for the undue delay in proceeding with the definitive procedure of ileocecal resection and consequent eradication of the underlying cause for the repeated intussusceptions.

In about 5 per cent of intussusceptions occurring for the first time a known mechanical etiologic factor is present. In a survey of 75 cases of recurrent intussusception Thorndike[6] observed that 14 (nearly 20 per cent) were due to a definite lesion of the ileum. With each additional recurrence one could predict an even greater likelihood that a causative lesion of the terminal ileum was present. On the basis of our recent experience and a survey of the literature, ileocecal resection seems warranted without further delay in patients with more than one recurrence of intussusception, regardless of whether an etiologic lesion of the terminal ileum can be found at the time of surgery.

The association of enlarged mesenteric lymph nodes with ileocolic intussusception is not unusual, although the exact significance of the lymphadenopathy is not understood. Hogg and Donovan[7] found enlarged mesenteric nodes in 11 per cent of their series. They suggested this might be part of a generalized lymphatic hypertrophy involving the terminal ileum and adjoining mesenteric lymph nodes, attributing the intussusception to the lymphadenopathy. Other observers have considered the mesenteric-lymph-node enlargement secondary to the intussusception. Stout[8] has cited an interesting case of intussusception in an infant subjected to ileocecal resection. Pathological examination revealed lymphoid hyperplasia in the submucosal region of the ileocecal valve characterized by large germinal centers whereas the adjoining enlarged mesenteric nodes did not exhibit this form of hyperplasia but rather a hyperplasia of the reticulum. Precisely the same situation obtained in the case presented above.

The localized lymphoid accumulations described above are somewhat suggestive of a similar process occurring within the rectum and variously known as "benign lymphoma," "lymphoid polyps" and "lymphadenoid polyps."[9-11] This condition, which appears to be a localized hyperplasia of the normal solitary lymph follicles in the rectal wall, may occur at any location within the rectum and presents as single or multiple polypoid areas ranging in diameter from 2 to 40 mm. Microscopically, the lesion is a nonencapsulated submucosal nodule composed of primary follicles with germinal centers. There is characteristically a pressure atrophy of the overlying mucosa, and the mucosal stroma shows a heavy infiltration of lymphocytes that are contiguous with the submucosal lymphoid masses. The lymphoblastic cells show numerous mitotic figures, and scattered reticular cells are present in a delicate meshwork of reticulum fibers. Although certain microscopical features of the lesion (absence of capsule and diffusion of lymphoblastic cells beyond the confines of the follicles) simulate those of a malignant process, the clinical behavior of the hyperplasia establishes it as benign, with no relation to the generalized lymphoid diseases.

Since the pathological alterations in the present

case had extended beyond the anatomic confines of the Peyer patches, the most difficult problem from the standpoint of pathological classification was to rule out the so-called giant-follicle lymphoblastoma, or Brill–Symmers disease. This is a condition characterized by an insidious onset of regional or general lymphadenopathy, splenomegaly, the absence of anemia or abnormal cells in the blood and marked radiosensitivity of the lesions.[12-14] Microscopical examination reveals complete replacement of the normal lymph-node architecture by follicles composed of enormously enlarged germinal centers. These centers are made up of lymphoblasts and prelymphoblasts. Significant numbers of nucleated cells do not appear, nor is there evidence of necrosis or inflammatory exudation. Surrounding each follicular nodule, the reticulum network is distorted and condensed by the expanding follicle, with the result that the pulp spaces become compressed and the interpulp spaces become elongated and narrowed. Capsular invasion and a tendency to fusion of adjacent follicles are invariably present. Giant-follicle lymphoblastoma is considered to be a condition borderline between lymphosarcoma and lymphatic leukemia and in its early stages is thought by some to represent a transition between hyperplasia and lymphosarcoma. It can be seen that the case reported above is a benign follicular hyperplasia and hypertrophy and lacks the architectural replacement, follicular fusion, reticulum condensation and sinusoidal blocking that characterize giant-follicle lymphoblastoma. It is also of interest that the enlarged mesenteric nodes on two different occasions showed a reticulum-cell hyperplasia without prominent follicular patterns, in no way similar to the process in the terminal ileum. Although the clinical course of the present case has tended to substantiate the microscopical diagnosis of benign lymphoid hypertrophy, it should be emphasized that in certain cases the differentiation of giant-follicle lymphoblastoma and hyperplasia of inflammatory origin is extremely difficult or impossible on histologic criteria alone.

Summary and Conclusions

The general problem of recurrent intussusception in infants and children is reviewed. The clinical and pathological findings in a patient who underwent five operative reductions of recurrent ileocolic intussusceptions, after which ileocecal resection was performed with success, are reported. The cause of the recurrent intussusception was a tumor mass in the terminal ileum that on microscopical examination proved to be characteristic of giant-follicle hypertrophy of Peyer's patches in the wall of the ileum.

The pathological features of this entity and its relation to the normal lymphatic apparatus of an infant, as well as to other diseases of the lymphoid system, are discussed.

On the basis of this case, together with a survey of the literature, ileocecal resection appears to be warranted if an ileocolic intussusception recurs more than once even though no tumor can be palpated within the terminal ileum.

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MEDICAL PROGRESS

EMERGENCE OF ANTIBIOTIC-RESISTANT BACTERIA*

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BOSTON

A NUMBER of reviews dealing with various aspects of the subject of microbial resistance to chemotherapeutic agents have appeared during recent years. Elizabeth McCoy's survey of the literature entitled "Changes in the Host Flora Induced by Chemotherapeutic Agents"[1] is quite pertinent. More recently Lepper[2] attempted to estimate the extent of the problem of antibiotic-resistant organisms as a cause of bacterial infections. The literature dealing with special aspects has also been considered — the problem of resistant staphylococci by Prissick,[3] Spink[4] and Clough,[5] the genetic factors by Bryson and Szybalski[6] and Bryson and Demerec,[7] streptomycin resistance by Miller and Bohnhoff,[8] and the more fundamental mechanisms concerned with the adaptation of microorganisms by a number of workers (reported in the *Third Symposium of the Society of General Microbiology*[9]). The aspects pertaining to replacement of the host's microflora by antibiotic-resistant species during antibiotic intake and bearing directly on problems encountered in agriculture have been incorporated in some of the extensive reviews on antibiotics in nutrition by Mickelson,[10] Braude,[11] Jukes and Williams,[12] Fidanza et al.,[13] Stokstad,[14] Knodt[15] and Jukes.[16]‡ This review will not consider most of the interesting problems concerning the mechanisms of development of resistance, or the fundamental genetic principles that evolved from the studies of resistance to antibiotics; these are dealt with in some of the reviews mentioned above. Nor will the subject that is even more pertinent to animal feeding and nutrition in general — namely, the mechanisms of the growth-enhancing effects of antibiotics — be reviewed in detail except as it bears on the problem of the residual antibiotic-resistant flora.

Any discussion of the emergence of resistance strains in vivo inevitably separates itself into two distinct parts, one dealing with the development of resistant strains of the same species and subtype as that originally present and demonstrated to be susceptible before exposure of the host to the antimicrobial agent, and the other concerning changes in the microflora resulting from the emergence, or attainment of a position of prominence or dominance, of resistant species after the suppression or elimination of susceptible elements of the microflora. Although the distinction is of both practical and fundamental importance, it is not always possible to discern it from many of the available reports because of the manner in which the data are collected or presented. From the points of view of clinical therapeutics and the individual patient, the first type of resistance is of the greatest importance although the second has also assumed considerable significance. The emergence of a resistant flora and increases in incidence of resistant strains or species of pathogenic organisms in the general population or in special groups of individuals are more important for the public health, and probably also in the use of antibiotics in animal feeding or in the processing of food. Since most of the data concerning the in vivo emergence of resistant strains of the same species in the primary host are derived from human clinical observations, and since I am more intimately acquainted with that phase of the problem, this presentation may, understandably, give greater prominence to experiences in human patients and relatively less attention will be devoted to problems in agriculture. The literature dealing with some of the properties of resistant strains will also be reviewed.

EMERGENCE OF RESISTANT STRAINS OF ORIGINALLY SENSITIVE SPECIES IN THE PRIMARY HOST

Some of the more extensive and detailed studies bearing on the development of resistant strains of specifically defined species of organisms in the original host and their spread within limited groups of individuals have dealt with pathogenic organisms, including Group A hemolytic streptococci *(Streptococcus pyogenes), Micrococcus pyogenes var. aureus (Staphylococcus aureus)* and *Mycobacterium tuberculosis.* Some of the pertinent observations on these organisms will be reviewed, and some reports of interest dealing with the emergence of resistant forms of other pathogens during the course of therapy will also be noted.

Str. pyogenes

The sulfonamide drugs and penicillin have been used successfully for several years in the prevention of infections with the hemolytic streptococcus and recrudescences of rheumatic fever. The early successes led to the large-scale use of the sulfonamides, mostly

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sulfadiazine, either for short periods or continuously for several months in several military installations during World War II in attempts to eliminate or minimize the occurrence of streptococcal and other susceptible infections. The over-all results have recently been summarized by Denny,[17] and those pertaining to the use of the sulfonamides by Wilson.[18] Strains of Group A streptococci resistant to the sulfonamides did not prove to be a problem when these drugs were administered prophylactically to rheumatic patients, but did when they were used extensively in military installations. Here, it was found necessary to administer the drugs continuously, for when sulfadiazine was discontinued, the incidence of streptococcal infections reached preprophylactic levels in a few days.[19]

The sulfonamide drugs were used most extensively in the United States Navy,[20] where more than 600,000 men received 0.5 to 1.0 gm. daily and an 85 per cent reduction in incidence of streptococcal infections and rheumatic fever was achieved. Sulfonamide-resistant strains of Group A streptococci appeared after sulfadiazine had been used in the Navy for less than a year. Subsequently, these strains and infections caused by them spread so rapidly and to such a degree that the chemoprophylaxis of streptococcal infections was finally abandoned.[21-23] The origin of these sulfonamide-resistant streptococci has not been determined, but continuous and extensive use in prophylaxis had apparently contributed to their spread. The sulfadiazine-resistant infections, however, were due entirely to streptococci of Group A, Types 17 and 19, whereas the other types continued to be sensitive.[21-23]

These observations point up the importance of the specific identification of the streptococci, since differences in sulfonamide sensitivity were associated only with certain specific types. Hamburger et al.,[24] in 1946, found no resistant variants among 45 carriers of a variety of types of Group A streptococci to whom they administered sulfadiazine for periods of four to fifty days. On the other hand, 13 per cent of 107 strains from 76 untreated carriers were found to be highly resistant; all these strains were Type 17, except for 1 that was Type 19. Gezon and his co-workers[25] more recently studied the sensitivity of beta-hemolytic streptococci from Navy recruits who received prophylactic penicillin or sulfadiazine for two weeks. There was no evidence of natural or acquired resistance to penicillin in Group A, or in Group B or C streptococci among 2262 strains. Tests for sulfadiazine sensitivity in 1681 strains of Group A yielded only 3 that were resistant; 2 of these were from the same person before and during sulfadiazine prophylaxis. There was therefore no evidence that sulfonamide resistance was acquired during the prophylactic administration of the drug. Sprague and Frank[26] tested the sulfadiazine sensitivity of 523 strains of hemolytic streptococci isolated at a Naval Training Station over a six-year period through 1954 and found only 6 that were resistant to 5 mg. per 100 cc. or more; 1 was a Group C strain, and the others were Group A — 4 of Type 5 and 1 untypable. Among the sensitive strains were 78 of Type 19, but none of Type 17. A recent study by Feldman[27] also indicates that in the years 1949-54 sulfadiazine-resistant strains were not encountered among 417 strains tested in Syracuse; these included strains of 15 specific types, including 33 Type 19 strains, and some that were untypable, but none of Type 17.

The experience in the military camps and the subsequent studies may therefore be interpreted as indicating that the problem of sulfonamide resistance is one of emergence and spread of sulfonamide-resistant strains of certain specific types of streptococci rather than the acquisition of resistance of previously sensitive ones as a result of continuous exposure to the drugs during their prophylactic use. The evidence for this, however, cannot be considered to be very conclusive.

Since 1946, penicillin has largely replaced the sulfonamides as the therapeutic and prophylactic agent of choice for infections due to the hemolytic streptococcus and for the prevention of rheumatic fever because penicillin has been shown to be more effective in eradicating Group A strains from carriers and from patients with streptococcal pharyngitis. Denny[17] concluded from the experiences with this antibiotic, as used in various ways and by many workers, that "no penicillin-resistant group A streptococci have yet been reported, but there has not been enough experience with prophylaxis over long enough periods of time in large groups to reach final conclusions concerning resistant strains."

An apparent exception was a report by Milzer et al.,[28] who, in 1948, recorded a high incidence of resistant hemolytic streptococci in rheumatic children receiving penicillin by mouth prophylactically. These penicillin-resistant strains, however, were not identified serologically, and subsequent studies by the same group of workers, reported in 1950[29] and 1953,[30] after the grouping of streptococci was included in their studies, failed to reveal any penicillin-resistant strains of Group A streptococci among such rheumatic children treated over long periods.

No significant resistance in Group A streptococci to chlortetracycline was encountered in a small group of rheumatic children given this antibiotic prophylactically for several months, although such organisms often were not eliminated during the antibiotic administration.[31] All hemolytic streptococci isolated during and after a six-week period while penicillin and chlortetracycline were used prophylactically in the course of an epidemic of streptococcal infections in a naval station remained highly sensitive to these agents, although they were not regularly eradicated by them.[32] This was also true in the early experience of Jackson, Lowbury and Topley,[33] with the use of

chlortetracycline in the prophylaxis and treatment of streptococcal infection in burns; penicillin-resistance likewise was not encountered in strains of *Str. pyogenes* cultured from burned areas treated with penicillin locally or systemically. Subsequently, however, Lowbury and Carson,[34] in the same clinic, reported finding 7 chlortetracycline-resistant strains from the burns of 5 patients. In 3 cases, chlortetracycline- and oxytetracycline-resistant strains (inhibited by 12.5 microgm. per cubic centimeter) were isolated after treatment with chlortetracycline, and streptococci of the same type (Type 9) spread from 1 of the patients to the burns of 4 others. Erythromycin was also used in the same types of cases, and, although streptococci reappeared in 3 of 24 cases after clearing, all strains were sensitive to erythromycin. Two other groups of workers[35,36] failed to demonstrate erythromycin-resistant strains of Group A streptococci in spite of their persistence or recurrence during antibiotic administration; this agent was used for prophylaxis in rheumatic fever[35] in one study and for the treatment of streptococcal infections and carriers in the other.[36] Smith et al.[37] noted only 1 patient in whom a hemolytic streptococcus increased in resistance to erythromycin—from 0.002 to 0.25 microgm. per cubic centimeter in five days.

It may be concluded from the observations on the use of sulfonamides and antibiotics in the treatment or prophylaxis of streptococcal infections that strains of Group A *(Str. pyogenes)* do not develop resistance as a result of exposure to these agents in human subjects. Thus far, strains of significant degrees of resistance to penicillin, the tetracyclines or erythromycin have not been encountered, except for the few isolated from infected burns; these strains were only moderately resistant, and it is not certain whether the same strains were originally present and sensitive before chlortetracycline therapy was started. At the Boston City Hospital, strains of Group A streptococci of even slight resistance to penicillin or the tetracyclines have not been encountered thus far,[38] and, except for some reports[28,39] of inadequately classified "hemolytic streptococci," some of which may have been of Group A, no authenticated strains of this group have been reported to be resistant to penicillin, erythromycin or the broad-spectrum antibiotics. Sulfonamide-resistant strains of certain specific types, mostly Types 17 and 19, remain the only authentic examples of *Str. pyogenes* of significant resistance to any of the important chemotherapeutic agents.

Str. viridans and Other Causative Organisms in Cases of Bacterial Endocarditis

A study of strains of the *Str. viridans* group obtained from the blood of patients with bacterial endocarditis at the New York Hospital[40] between 1944 and 1954 revealed no change in the susceptibility to penicillin, the agent most widely used in the treatment of such infections. Another recent report by Hamburger and Carleton[41] showed that the rate of killing of the organisms and the time required for penicillin in the same concentration to sterilize cultures were similar for strains of *Str. viridans* obtained from patients with bacterial endocarditis who were treated successfully and from those who relapsed after a course of penicillin treatment. Balme and Dormer[42] reported 2 cases in which *Str. viridans* and *Str. faecalis* retained their original susceptibility during several weeks' treatment with broad-spectrum antibiotics; the patients responded later to penicillin alone in the first case and combined with streptomycin in the other.

Increases in penicillin resistance of different causative organisms during treatment of bacterial endocarditis or during relapses after treatment with this antibiotic have been encountered,[43-47] but many, and perhaps most, of the relapses and failures have not been associated with the development of resistant organisms.[48-51] Some of the increases in resistance that were significant were observed in strains of *Str. faecalis,*[47,52,53] but those in *Str. mitis* or in other strains of the viridans group were not marked,[49,54-56] although an occasional strain apparently increased as much as 100-fold.[49,57] Among the cases collected in a joint study by the Medical Research Council, only 15 of 65 strains of *Str. viridans* from patients in relapse showed increases in penicillin resistance: 7 had increased 3-fold or less, 7 others 4-fold to 10-fold, and 1 160-fold. There was some question whether the last was the same as the original strain or represented reinfection with a different strain or species, since it was not classified further. Acquired resistance was uncommon in the experience of Loewe[44] among 157 cases observed before 1950.

In a recent review on the treatment of bacterial endocarditis,[58] the reports of increased resistance of the causative organisms during the course of treatment with antibiotics other than penicillin were summarized. It is interesting that of over 150 patients treated with streptomycin, only 4 were definitely noted as having organisms that increased in resistance to that agent during treatment, but in only 1 case was the increase of great magnitude; that was in a strain of *Gaffkya tetragena* that was quite sensitive when treatment was started.[59] Most of the patients, however, received other antibiotics in addition to the streptomycin. Among 43 patients in whom chlortetracycline failed to bring about a cure, the failure was associated with a significant increase in resistance (from 5 to 40 microgm. per cubic centimeter in three days) in only 1 case, but in another an apparent increase in chlortetracycline-resistance from 0.09 to 25 microgm. per cubic centimeter was reported as occurring during therapy with penicillin alone, although the patient had received chlortetracycline before the first strain was obtained. Four-fold or greater increases in oxytetracycline resistance of streptococci during therapy with that antibiotic were noted

in 3 patients, and the minimum inhibiting concentration of oxytetracycline for a staphylococcus obtained from the blood on successive occasions increased from 0.25 to 2.5 microgm. per cubic centimeter during a course of treatment of a case of endocarditis with chlortetracycline. Oxytetracycline resistance increased 50-fold during treatment in a strain of *M. aureus*.[60] Increases in resistance of *Staph. aureus* to chloramphenicol during treatment of bacteremic patients with that agent was described by Astler and Morgan,[61] and Bunn and Cook[62] reported that a paracolon bacillus, originally sensitive to chloramphenicol and streptomycin, became totally resistant to 6 agents, alone or in combinations.

All but 1 of the 12 collected cases of failure of bacterial endocarditis to be cured by erythromycin[58] were associated with increases in resistance of the causative organisms that were isolated from the blood (3 *M. aureus*, 1 *Str. viridans* and 1 *Str. faecalis*). In a more recent report from the Mayo Clinic,[63] 6 of 7 patients treated for endocarditis with erythromycin failed to respond; available data on the sensitivity of the strains from 4 of these patients indicated that 3 of these 4 failures were accompanied by increased resistance developing in originally sensitive strains (1 of *Str. mitis* and 2 of *M. pyogenes*). Roantree and Rantz[64] noted rapid development of erythromycin-resistance of *M. aureus* in a fatal case. Field and Taylor[65] reported that 3 strains of *Str. viridans* became resistant to carbomycin after treatment with that antibiotic for ten, eighteen and thirty days, respectively; the source of the organisms and the disease that was treated were not mentioned, although they presumably were cases of endocarditis.

These findings have been detailed here because of the particular significance of cases of bacterial endocarditis as representing examples in which successive strains of organisms are most probably derived from the original ones that were present before treatment was started. They indicate that, although the acquisition of increased resistance to antibiotics during treatment appears to be an important factor in some cases, it occurs infrequently with most of the antibiotics and is probably not a common cause of failures to cure this disease except in cases treated with erythromycin. The combined use of multiple antibiotics may have delayed or prevented the development of increased resistance in many patients, particularly in those receiving streptomycin, since a large proportion of the patients with bacterial endocarditis received multiple agents; such combined therapy, however, does not always prevent the development of resistance to erythromycin.[66]

M. aureus

The greatest number of detailed clinical, bacteriologic and epidemiologic data reflecting the impact of extensive and continuous use of antibiotics in clinical medicine concern the change in antibiotic resistance of pathogenic staphylococci. Although the Oxford workers,[67] in 1941, first demonstrated that cultures of staphylococci could be made resistant by continuous subculture in the presence of the antibiotic in vitro, it was Rammelkamp and Moxon[68] who, in 1942, first observed an increase in resistance of 4 strains of staphylococci isolated from patients during the course of treatment of localized infections with penicillin. Slight increases in penicillin resistance during treatment were noted by others[69-72] in the early days of the use of penicillin, among strains of staphylococci isolated from hospitalized patients. In 1944, Garrod,[73] like others, reported the finding of occasional strains of abnormal resistance to penicillin: "this was sometimes a property of the original culture, but more often it developed during treatment, clearly owing to habituation; there was corresponding failure of clinical progress." Failures of penicillin therapy in infections with resistant staphylococci were also noted early by Plough.[74] The Oxford workers[67] showed that resistance that had been acquired in vitro was not due to any penicillin-destroying enzyme in the medium or in the cells. It was Bondi and Dietz,[72,75] however, who demonstrated that the ability to produce penicillinase is not acquired by staphylococci that are made resistant in vitro or in vivo but that penicillinase is a property of strains of staphylococci that are naturally resistant to penicillin.

Mary Barber, in England, was the first to call attention to the problem of the increasing occurrence of penicillin-resistant staphylococci in hospitals in a series of papers beginning in 1947[76-80]; she also studied the characteristics of these strains extensively.[79,81-84] Spink and his co-workers[4,85-88] were also among those who showed early and continuous interest in this problem and studied both the occurrence of antibiotic-resistant strains and their properties in vitro and in vivo. The literature dealing with penicillin-resistant staphylococci before 1949 was reviewed by Chain et al.,[89] and later studies of resistance of staphylococci to various antibiotics were noted above in the opening paragraph.

Numerous other investigations of the increasing occurrence of staphylococci resistant to penicillin and to the other widely used antibiotics as they became available have been reported from many hospitals and laboratories in the United States,[28,90-98] Canada,[99-101] Australia,[102-107] Norway,[108-113] Sweden,[114-116] Denmark,[117] France,[118-121] India[122] and Chile.[123] Additional studies bearing particularly on epidemiologic aspects, most of them involving identification of the bacteriophage types of the staphylococci and observations in diverse groups having varying degrees and types of exposures to antibiotics, have been reported, chiefly by the same workers and also by others in England,[78,80,124-133] Australia [134] and the United States.[2,87,135-142] The importance of antibiotic-resistant staphylococci as secondary invaders and causes of superinfections during antibiotic therapy of infec-

tions with other organisms has also been noted by several groups.[142,144-147] Emphasis has been placed, in some studies, on the importance of the development of resistance in staphylococci to erythromycin in vitro[66,148-150] and during treatment,[37,66,87,150-155] and to the crossresistance between erythromycin and carbomycin.[148-150] The increasing incidence of erythromycin-resistant staphylococci in hospital patients and personnel and in the community accompanying the extensive use of this agent has also been reported by Lepper and his associates,[96,156] Resseler[150] and Wise et al.[87,154,155] The persistence of antibiotic-resistant strains acquired by patients in the hospital after discharge and the spread of such strains to family contacts was reported by Dowling, Lepper and Jackson.[157] Data bearing on the clinical implications of the resistant strains have also been presented by a number of observers from surgical wards and other types of hospital and outpatient clinics.[3,4,87,90,127,158-166] A few observations in animals[167-169] have indicated that resistant staphylococci play only a minor part in the failure to cure bovine mastitis. This was noted by Schalm and Ormsbee[167] in 1949 and reaffirmed by Schalm and Woods[168] in 1953 and by Alford, Lusi and McCrary[169] in 1955.

The studies dealing with antibiotic-resistant staphylococci (only pathogenic strains that are hemolytic and produce coagulase are generally considered) may be summarized briefly:

The percentage of penicillin-resistant staphylococci isolated from patients in large hospitals in many countries has increased steadily in the past few years so that now nearly three fourths of all strains are highly resistant to penicillin.

Penicillin-resistant strains are found not only in suppurative lesions under treatment with this antibiotic but also in the noses and throats in similar proportions from patients in the same hospital who are not receiving penicillin — and frequently in the feces of such patients.

The percentage of penicillin-resistant staphylococci increases markedly during the period of hospitalization both in patients who receive penicillin in the hospital and in those who do not, although penicillin therapy results in somewhat earlier and more frequent appearance of the resistant strains.

The hospital staff and personnel carry staphylococci of the same bacteriophage types as the patients, and a similar proportion are resistant to penicillin.

Phage typing of staphylococci from patients and staff indicates that the organisms are acquired by crossinfection from other patients and from the hospital personnel (chiefly the latter).

Penicillin-resistant staphylococci are much less frequent (about a half to a third) among outpatients than among inpatients; among the outpatients the incidence is related to the amount of previous penicillin treatment or of previous hospitalization, or both.

The incidence of strains resistant to penicillin among the general population is still lower than that among outpatients, and this too is related to previous treatment and hospitalization. At the time of admission to hospitals, patients have a higher carrier rate of penicillin-resistant staphylococci than people in the community at large.

Although there are no good data on the resistance of staphylococci among patients who are treated at home, there is evidence that such treatment results in an increased occurrence of resistant strains; this is based on the higher proportion of such strains among patients subsequently coming to the outpatient clinics or admitted to hospitals, as compared with that in the population at large.

When studies have been carried out in areas where very little antibiotic therapy is used, resistant staphylococci from infected lesions or from carriers are generally infrequent.

Resistance of the staphylococci is generally much lower to the tetracycline antibiotics than to penicillin, but in hospitals where they have been used very extensively, the incidence may approach that of penicillin-resistant strains during periods of intensive use. Usually, tetracycline-resistant staphylococci are about half as frequent as the penicillin-resistant ones.

Erythromycin-resistant strains of staphylococci rapidly appear in hospitals where that antibiotic is used; both the degree of resistance and the incidence of resistant strains appear to increase with such use even more rapidly than with earlier antibiotics, and the number of erythromycin-resistant strains within a brief period may reach or even exceed that of penicillin-resistant strains during periods of intensive use.

The incidence of strains resistant to individual antibiotics is related to the extent to which each is used.

The frequency with which strains resistant to multiple antibiotics are encountered is similarly related to the extent to which the particular antibiotics in question are used.

Increases or decreases in the amounts and intensity with which any given antibiotics are employed may be associated with changes in the same direction in the incidence of staphylococci resistant to those antibiotics.

The simultaneous use of antibiotics in combinations has been recommended as a means of preventing the development of resistant strains of staphylococci. Data reflecting the results of combined therapy are scanty but thus far indicate only the possibility of depressing, delaying or avoiding the appearance of resistant strains in individual patients; there is no evidence as yet that the incidence of resistant strains is reduced by combined therapy.

The increasing occurrence of staphylococcal infections within hospitals and the decreasing effectiveness of the available antibiotics in the treatment of such infections is being widely appreciated and, in many hospitals, is reaching serious proportions.

It is interesting that in the early studies on the susceptibility of staphylococci to penicillin, the range of concentrations to which different strains were susceptible was narrow. Indeed, strains of staphylococci resistant to more than 10 units per cubic centimeter were not encountered in the first few years,[93] whereas in recent years most of the resistant strains grow freely in very high concentrations, usually more than 400 microgm. of penicillin per cubic centimeter, and there are relatively few strains of intermediate resistance.[38,94] Although resistance to similar concentrations of penicillin are attainable by proper subcultures of penicillin-sensitive staphylococci in increasing concentrations of the antibiotic, it is rare to encounter changes of similar degree developing in originally sensitive staphylococci under conditions that reasonably ensure the exclusion of new intruders from extraneous sources.

Moreover, the originally sensitive strains that develop resistance in vitro or in vivo do not produce penicillinase,[72,75] and their resistance is considered not to be so permanent as that of resistant staphylococci isolated from patients.[4,86,170] Unfortunately, data on penicillinase production by the strains described in studies before the availability of penicillin are not available, but resistant strains isolated and tested since that time have all proved to be penicillinase producers. Some enterotoxin-producing strains of staphylococci isolated before penicillin became available have been shown to be highly resistant to penicillin, but their ability to produce penicillinase was not tested.[171]

The clinical and epidemiologic evidence all seems to corroborate the early conclusion of Bondi and Dietz[72,75] that the production of penicillinase by staphylococci and its association with penicillin resistance are a "natural" trait. However, the possibility cannot be excluded that the increase in the degree of resistance of many such strains resulted from some previous exposure to the antibiotic. Nevertheless, the change observed in patients who when first seen have highly sensitive staphylococci and then, either with or without penicillin treatment, rapidly acquire organisms of very high degrees of resistance must be interpreted as the acquisition of new, naturally resistant strains. It is of interest that the initial increases in penicillin resistance to high levels occurred after 1946[93] and coincided with a change in the general usage of penicillin from small or moderate to very large amounts, and also from small to large doses in individual patients, as the antibiotic became more widely available and inexpensive.

It is possible that natural resistance of staphylococci to the tetracycline antibiotics also occurs and is responsible for the rapid acquisition of strains of high degrees of resistance to those agents,[94] although in this instance substances inhibiting these antibiotics have not been demonstrated in the resistant strains or their products. The experiences with erythromycin,[96] however, suggest a direct effect of exposure of the organisms to that antibiotic as the factor responsible for the acquisition of resistance by staphylococci within the treated patient in the first instance, and then among groups of patients and their contacts, in whom erythromycin is intensively used. Available reports on erythromycin and, indeed, on chlortetracycline (the first of the agents of the tetracycline group to be introduced) indicate that all the strains of pathogenic staphylococci were susceptible to a narrow range of low concentrations before these agents were introduced and, at least with erythromycin, steady increases both in the degree of resistance and in the incidence of resistant strains have been demonstrated, and this was true both in the patients treated with the antibiotic and in those acquiring erythromycin-resistant strains from others.[96,154] This phenomenon may also have occurred when chlortetracycline was first introduced and while it was achieving wide use, but there are no adequate studies demonstrating a clear progression in the degree of chlortetracycline resistance in any given population. Nevertheless, the changes in the incidence and degree of resistance of staphylococci to chlortetracycline as observed at the Boston City Hospital are qualitatively similar to those that occurred with penicillin.[38,93,94]

Mycobacterium tuberculosis

The development of resistance of tubercle bacilli to antimicrobial agents is of interest for various reasons. In the first place, treatment is usually of long duration. The number of really effective agents in general use is small, and these all have the property of inducing resistance in tubercle bacilli in vitro and in vivo. Except for streptomycin (and possibly cycloserine) these agents are not effective against other elements of the flora and are not used in the treatment of other infections. It may be assumed with considerable, although not absolute, assurance that any increase in resistance demonstrated in tubercle bacilli isolated during treatment resulted from exposure of the organisms to the appropriate agents. The subject has received carefully controlled study by many competent workers. There is a considerable body of data available on the effect of combinations of the active therapeutic agents. The subject as it relates to streptomycin was reviewed in 1949 by Steenken and Wolinsky,[172] and, as it relates to the 3 major drugs available up to 1954, by Mitchison.[173]

Resistance of tubercle bacilli to streptomycin increases progressively in the course of continuous treatment with this agent,[174-176] and this may continue for a time after treatment is stopped.[174] Sensitive organisms may be obtained along with the resistant ones.[176]

The proportion of patients in whom resistant strains emerge when the tubercle bacilli are not eradicated likewise increases progressively with increased duration of treatment.[174,175] The development of resistant strains and their incidence are also influenced by a number of other factors: the nature of the pathologic lesion, particularly the presence of large and old cavities that persist[177-179]; previous treatment with the drugs[179]; the dosage regimen,[177,178,180,181] including the interval between doses[181,182]; and the use of other active agents, particularly para-aminosalicylic acid (PAS) and isonicotinic acid hydrazide (isoniazid, INH).[173,179,183-188] Strains that are sensitive in vitro[180,189,190] and in vivo[190] have been obtained from patients after they had shed resistant ones for long periods. Streptomycin resistance of tubercle bacilli, once acquired during treatment, persists,[191] as does the virulence of the organisms both for man[190] and for guinea pigs[192,193] and mice.[194] Patients with streptomycin-resistant strains respond poorly to subsequent treatment with this agent alone or in combination with other drugs,[173,179] but the organisms remain fully sensitive to PAS and INH.[173] Tubercle bacilli that were highly resistant to neomycin have been found in one kidney when strains isolated (after prolonged treatment with this antibiotic) from other organs at the same time were very sensitive.[195]

Para-aminosalicylic acid has a low degree of therapeutic effectiveness when used alone, and tubercle bacilli acquire resistance during such treatment more slowly,[183,196] to a lower degree and less frequently[174,180] than to streptomycin alone but streptomycin-resistant strains retain their sensitivity to PAS.[196] This drug, however, has the property of delaying and depressing, but not entirely preventing, the emergence of resistance to streptomycin.[179,183-185] Continuous administration of the PAS is required to obtain this effect,[179] whereas streptomycin given twice weekly instead of daily or more often is more effective in suppressing streptomycin resistance, whether the antibiotic is used alone or with PAS.[179] The organism must be originally sensitive to both agents for this delaying or depressing effect to occur,[179,187,197,198] but even the combined drugs may fail to affect the development of resistant strains in far advanced cases.[179,199] PAS-resistant strains are fully virulent for guinea pigs, and infections with such organisms are not affected by treatment with PAS, either in guinea pigs or in man.[173] It is interesting that strains of moderate or high resistance were only rarely found in mice treated with streptomycin, with or without PAS, in guinea pigs treated with streptomycin or in rabbits treated with streptomycin with or without viomycin for prolonged periods.[200]

The development of resistance in tubercle bacilli to INH during treatment with that agent alone occurs in man in the same manner as was noted for treatment with streptomycin alone[180,201] or even more readily.[202] In some patients, INH resistance of tubercle bacilli apparently continues to develop and increases for a time after treatment with INH is stopped.[203] When INH is used along with streptomycin in the treatment of pulmonary tuberculosis, a larger number of patients become free of demonstrable tubercle bacilli in their sputum, but in those in whom the organisms persist, the development of resistance to the antibiotic is delayed and depressed as it is when streptomycin is given with PAS,[179,188] and perhaps slightly more so during the first few months of treatment.[203] Treatment with streptomycin in combination with INH also depresses the development of INH-resistant strains, although less than treatment with the combination of INH with PAS.[179] Here, again, the organisms must be originally sensitive to both agents of the combination for any delaying or suppressing effect on the emergence of resistance to either agent to occur.[173,187,189] PAS delays the emergence of INH as well as it does streptomycin resistance,[179] and the relative doses used may be important.[204]

Unlike tubercle bacilli resistant to streptomycin or PAS, which retain their virulence for man and animals, those resistant to INH lose their virulence for guinea pigs in proportion to their increase in resistance in vitro[173,205-210] but retain their virulence for mice.[173,207-211] Patients with INH-resistant organisms or mice infected with such strains derive little or no benefit from treatment with this drug,[212] but evidence for this has been considered inconclusive.[213] After cessation of treatment with INH the resistance of the tubercle bacilli may increase or decrease,[202] or sensitive strains may again be obtained.[203,214] There is evidence that INH resistance may be unstable in vitro,[215] but high degrees of INH resistance may be accompanied by loss of the ability of the organisms to produce catalase, which in turn is associated with loss of virulence for guinea pigs.[173,206,216-219b] Peizer et al.[220,221] confirmed the loss of virulence of tubercle bacilli that became INH resistant during treatment[220] and found a good correlation between catalase activity and guinea-pig virulence[221] but no agreement between the INH-resistant results with either their catalase activity or their degree of guinea-pig virulence. They found no one significant concentration at which cultures became nonvirulent for guinea pigs or catalase negative.[221]

Resistance of tubercle bacilli to antituberculous drugs arises primarily in patients under treatment with these agents and can be expected to be important in the response of those patients to further treatment with the same agents. Have they any broader significance for the public health? Since tubercle bacilli persist after treatment most often in patients with large cavities, and it is in just such patients that resistant organisms develop with considerable frequency after therapy, it may be anticipated that these organisms would be transmitted to contacts and thus constitute a public-health hazard.

Drug-resistant strains of tubercle bacilli in patients who have, themselves, not received treatment with antituberculous drugs have been quite infrequent. Isolated cases have been reported[222,223] in persons caring for tuberculous patients in sanatoriums. Wilking et al.[224] demonstrated tubercle bacilli resistant to 10 microgm. of streptomycin per cubic centimeter in 5 of 115 children under thirteen years of age before they had received any antibiotic, but details concerning the source of the infection in these children were not given. Thomas and his associates[225] also reported 9 cases in which drug-resistant tubercle bacilli were obtained from patients not previously treated with the relevant drug. The infection showed primary resistance to streptomycin in 4, to PAS in 4 and to both in 1. The infection in 3 and possibly 4 of these patients was known to have been present before these drugs came into general use; the original organisms in these cases were presumed to have originally been sensitive and the patients subsequently superinfected with resistant bacilli. Youmans and Williston[226] demonstrated tubercle bacilli resistant to 6 to 1000 microgm. of streptomycin per cubic centimeter in cultures from 9 of 14 patients who had never received streptomycin.

In 1951, Ferebee and Appel,[227] in the course of a co-operative study on the chemotherapy of tuberculosis, encountered 18 patients whose initial cultures yielded streptomycin-resistant tubercle bacilli; only 5 of them had previously been treated with the antibiotic. A more intensive study of the prevalence of resistant tubercle bacilli was reported by Cummings and Livings,[228] who analyzed the results of sensitivity tests in 5524 consecutive admissions to 30 hospitals over the period of seven months ending December, 1953. Among 1166 who had themselves never received streptomycin 30, or 2.6 per cent, had resistant tubercle bacilli, and 17 of these 30 had definitely been exposed to tuberculous patients who had been hospitalized after 1946. All but 5 of these patients were treated with combinations of streptomycin and either PAS or INH, and the majority responded favorably to such treatment.

In another study on the prevalence of streptomycin-resistant and INH-resistant strains of *Myco. tuberculosis* in patients with newly discovered and untreated active tuberculosis, Chaves et al.[229] found some degree of resistance to one or both in 11.2 per cent of 385 positive specimens. A history of exposure to previously treated active cases was obtained in only 5 of these patients. Only 1.2 per cent had a significant degree of resistance to streptomycin, and 2.3 per cent to INH, but none were resistant to both. Beck,[230] more recently, reported drug-resistant tubercle bacilli in only 10 (less than 2 per cent) of 600 newly diagnosed cases, and a presumptive source of contact was determined in 8 of them; 1 of the patients recovered without chemotherapy, and 8 responded favorably to multiple chemotherapy, including streptomycin.

Youmans,[231] in a recent comment on this problem, pointed out that the low incidence of new infections due to drug-resistant tubercle bacilli may be related to the use of combined therapy, to the possibility that resistant strains are less pathogenic or have less chance of producing progressive disease, or to few opportunities for contacts because treatment was almost entirely in hospitals. The effect of domiciliary and outpatient treatment might increase the number of patients potentially disseminating resistant strains; the problem would then become one of the pathogenicity and invasiveness of such disseminated strains and the care given to avoid contacts by isolation precaution.

Earlier, Welch[232] made the following observation:

> The emergence of resistant tubercle bacilli following the use of isoniazid could constitute a public health problem, particularly if the drug is used indiscriminately . . . When the drug was released for use, it was recommended by the Food and Drug Administration . . . that it be used only for those patients with tubercle bacilli resistant to streptomycin. Some question may arise concerning the advisability of such a procedure. The use of isoniazid alone in such cases may well result in the emergence of strains resistant to the drug in relatively short periods of time, giving the patient only temporary benefit and making him a reservoir of isoniazid-resistant strains, thus extending a public health problem initiated by streptomycin.

A study of oral antimicrobial therapy of nonhospitalized patients with tuberculosis was undertaken by workers in the Department of Health of New York City.[233] They encountered INH-resistant bacilli in 7 of 82 patients in whom proper studies were made. Although they do not consider this to be serious, this may represent an important reservoir of infection and certainly bears watching in view of the conclusions drawn by the previously cited workers[227-230] and by others, on the basis of their earlier observations,[234] that drug-resistant tubercle bacilli do not, at present, constitute an important public-health problem.

No mention was made of other antituberculosis drugs, such as the sulfones, viomycin, pyrazinamide, oxytetracycline and cycloserine, all of which at present have only a very minor role in the treatment of human tuberculosis. The tetracycline drugs, however, may be mentioned briefly because they are used so widely in other infections. Oxytetracycline was shown by Hobby and Lenert[235] to have antituberculous activity in vitro and in vivo against both streptomycin-sensitive and streptomycin-resistant strains, and this was confirmed by Steenken and Wolinsky[236]; both reports indicated that resistance to this agent develops slowly. When used together with streptomycin in two clinics, oxytetracycline was considered to have an effect similar to that of PAS in depressing the emergence of resistance to streptomycin.[237,238] More recently, Hobby and Lenert[239] noted that tetracycline was slightly more active than either oxytetracycline or chlortetracycline in vitro, but that the activity of the 3 tetracycline antibiotics against tuberculous infection in mice was indistinguishable. All 3 have the advantage of being more active in an acid medium. No data are avail-

able on the prevalence of strains of tubercle bacilli resistant to these agents.

Other Specific Causes of Infections

The organisms discussed thus far are the ones for which the largest amount of documented information is available. There are also a number of reports concerning the development of resistance in other species of pathogenic micro-organisms during antimicrobial treatment of infections in which they are considered to be etiologic; some of these may be considered briefly.

Neisseria and brucella. After the widespread use of sulfonamide drugs, a large and increasing proportion of cases of gonorrhea failed to respond to treatment with these agents, and the failures were associated with sulfonamide-resistant strains of *Neisseria gonorrhoeae;* there was, however, no demonstration that any originally susceptible strains became resistant during treatment with these drugs.[240] It is interesting, therefore, that Schmith and Reymann[241] (cited by Miller[242]) found some strains that were sulfonamide-resistant among 50 old laboratory cultures of *N. gonorrhoeae* isolated from patients in the presulfonamide era; these were as resistant as any that were later recovered from patients who failed to respond to treatment with sulfonamides. Recent observations[243] suggest that, at least in Boston, the incidence of sulfonamide-susceptible strains of *N. gonorrhoeae* may actually have increased significantly between 1949 and 1954, a period in which penicillin almost completely replaced sulfonamides in the treatment of such infections. The extensive use of penicillin for gonorrhea and other infections has not resulted in the appearance of any authentic reports of penicillin-resistant strains of gonococci,[38,243-248] even when penicillin was used prophylactically[245] and the rare cases in which they have been described[249-251] either are open to serious question[156,251] or the differences noted were within the error of the methods used.[245,246] Even strains from cases alleged to be therapeutic failures have been found to be highly sensitive.[243-246] Gonococcal strains of increased resistance to other widely used antibiotics likewise could not be demonstrated.[243,244] The editorial warning[252] of the danger of increased penicillin resistance from prophylaxis seemed quite reasonable, but, so far, this danger has not been manifest.

Resistance of *N. meningitidis* to penicillin was not encountered in a recent study,[253] and a few strains that were apparently resistant to sulfadiazine in vitro were not associated with therapeutic failures and were susceptible to the drug in experimental infections of mice.[254] Antibiotic resistance of strains of *Brucella abortus* have been reported only in a case of subacute bacterial endocarditis[255] in which a streptomycin-resistant strain was obtained from blood cultures; antibiotic resistance was not encountered by Spink[256] as a cause of therapeutic failures or relapses after treatment, by 1949,[256,257] or subsequently.[258]

Salmonella. Strains of salmonella, including *Salmonella typhosa,* are notoriously difficult to eradicate with antibiotics, even with the use of large doses of streptomycin, chlortetracycline or chloramphenicol given orally or parenterally in prolonged courses, in spite of the fact that strains of these organisms are at least moderately sensitive to all these agents in vitro. Failure to eradicate these organisms either from patients with active infections or from carriers has not been associated with the development of any degree of increased antibiotic resistance of the strains during or after treatment.[259-266a]

Pseudomonas and proteus. Stanley,[266b] in 1947, called attention to the growing importance of pseudomonas infections, and later Yow[267] called attention to the increasing importance of antibiotic-resistant strains of proteus and pseudomonas among infections encountered in a hospital. He urged discontinuance of ineffective antibiotics to permit re-establishment of the normal flora. Strains of *Pseudomonas aeruginosa* isolated in Boston in 1954[268] showed a significant increase in the proportion resistant to streptomycin, chlortetracycline, tetracycline and neomycin, as compared with strains isolated there in 1949; there were no changes, however, in resistance to polymyxin, erythromycin, chloramphenicol, bacitracin and also, interestingly enough, oxytetracycline. The increased resistance to neomycin and tetracycline was considered to be related by crossresistance (as discussed below) to corresponding changes in resistance to streptomycin and chlortetracycline respectively, since neither neomycin nor tetracycline had been used before these studies.[268]

There are probably no authentic cases of strains of *Ps. aeruginosa* resistant to polymyxin although half of 68 strains studied in Chile were so classified.[269] Sherwood et al.[270] tested 15 strains classified by others as being resistant to polymyxin B sulfate and found that all had been improperly tested, incorrectly identified or incompletely purified (that is, some were found to be mixed with polymyxin-resistant species). All the strains tested were inhibited by 5 microgm. per cubic centimeter or less, and this has been the general experience.[268,271,272]

Species differences are important when resistance of strains of proteus to various antibiotics is compared. Thus, Potee et al.[273] found that most strains of *P. mirabilis* were inhibited by 100 microgm. or less of penicillin per cubic centimeter whereas strains of *P. vulgaris, P. morganii* and *P. rettgeri* grew uninhibited in 400 microgm. On the other hand, almost all strains of *P. mirabilis* were resistant to 400 microgm. of oxytetracycline or chlortetracycline and required 100 or 200 microgm. of tetracycline per cubic centimeter for inhibition, whereas two thirds of the strains of the other 3 species were inhibited by 12.5 microgm. of all three tetracycline antibiotics. Strains of *P. mirabilis* were also somewhat more susceptible to chloramphenicol than those of other species. Some apparent increases in resistance to penicillin, strepto-

mycin, the tetracyclines and chloramphenicol were demonstrated in strains of proteus isolated in 1954 as compared with those isolated and tested in 1949; some of these differences, however, may have been related to differences in the proportion of strains of the different species in the two series.[273] Perch,[274] in Copenhagen, showed a correlation between antibiotic susceptibility and the species of proteus; also, in his study, strains of the same serotype behaved uniformly. Among strains of providencia, those that were inositol positive were all resistant to various antibiotics.

Klebsiella. Eisenberg et al.[275] noted a similar relation between serologic types of *Klebsiella pneumoniae* and their susceptibility to various antibiotics; Types 1 and 4 (formerly, A and D) were the most sensitive; Type 7 was the least sensitive, and others were intermediate.

Miscellaneous species and surveys. Kenney, Johnson and Tatz[39] reported the results of 12,333 tests for sensitivity done from 1949 to 1952 in New York on organisms isolated routinely in a hospital laboratory, employing a standardized paper-disk technic. They observed a steady increase in the percentage of penicillin-resistant strains of *Staph. aureus* and *Staph. albus* to the middle of 1952 and some decline in the latter part of that year. Also, the proportion of alpha streptococci resistant to penicillin increased steadily from 0 to 62 per cent, and that of "beta streptococci" from 0 to 58 per cent, but there was no difference in the gamma streptococci. The percentage of strains resistant to chlortetracycline and oxytetracycline rose during the period for all strains except *Staph. albus* and aerobacter species. There was no great increase in the proportion of strains of gram-positive cocci resistant to streptomycin during this interval, but the gram-negative bacilli did show increases. Against chloramphenicol, the percentage of resistant strains rose between 1949 and 1951, but dropped appreciably for 7 of the 11 species studied during 1952, coincident with a decline in the use of this agent.

Schneierson [276] and Weil and Stempel[277] reported similar studies from New York City. The former tabulated the results of tests for sensitivity to chlortetracycline and chloramphenicol during the three years 1949 to 1951; he found a gradual emergence of resistance to chlortetracycline in *Escherichia coli,* proteus, *Staph. aureus, Staph. albus* and *Str. faecalis* and some increase in the percentage of strains of *Esch. coli, Ps. aeruginosa* and proteus resistant to chloramphenicol. Weil and Stempel found no general rise in the percentages of strains resistant to the individual antibiotics among strains isolated in a routine hospital laboratory in 1953, as compared with those studied from 1950 to 1952. There was, however, an apparent increase in the proportion of strains of proteus and possibly of pseudomonas sensitive to chloramphenicol. There was also some improvement in strains "resistant to all antibiotics"; in 1950-52 about 14 per cent of 330 strains were so classified and nearly half these were pseudomonas, whereas in 1953, when polymyxin and erythromycin were also included in the tests, only 2 of 182 strains were resistant to all antibiotics. Subsequently, the same authors,[278] after studying 1117 additional strains isolated during twelve months in 1953-54, concluded: "By and large the trend to increased resistance to the commonly used antibiotics has come to a halt."

In Copenhagen, Lund[279] reported that from 1947-48 to 1949-51 the number of penicillin-resistant *Staph. aureus* rose from 16 to 59 per cent and those resistant to sulfonamides from 22 to 72 per cent. In the latter period, 96 per cent of all gram-positive cocci and 72 per cent of all gram-negative bacilli were sensitive to chlortetracycline, oxytetracycline and chloramphenicol. Among nonhospitalized patients in the Paris area, Chabbert et al.[110] noted a steady increase in the percentage of strains of staphylococci resistant to penicillin, from about 12 to 68 per cent between 1948 and 1952; those resistant to streptomycin, chlortetracycline and chloramphenicol showed a smaller but also definite rise. They observed no increases in resistance to any of these antibiotics among streptococci, coliform bacilli, proteus and *Ps. aeruginosa* isolated from similar patients during the same period.

No increases in resistance to any of the clinically useful antibiotics have been noted among pneumococci,[109] or *Haemophilus influenzae*[280] collected in different years at the Boston City Hospital.

Of interest is a report by Kirby et al.,[281] who found gram-negative bacilli resistant to all of 5 antibiotics (streptomycin, chlortetracycline, oxytetracycline, chloramphenicol and polymyxin B) in the urine of 117 (17 per cent) of 700 patients whose cultures were positive. The patients were mostly of the older age group and had indwelling catheters. The organisms were classified in the achromobacter group and were considered to have become pathogenic as a result of catheterization and antibiotic therapy.

Animal Diseases

A detailed review of the literature on this aspect was not made. Catron,[282] however, noted reports that some organisms become resistant to antibiotics used at therapeutic levels, but under practical conditions, in life-cycle feeding, there was no evidence of drug fastness. Bornstein and Samberg[283] observed that in about a third of birds inadequately treated with streptomycin for infectious coryza, streptomycin-resistant strains of *Haemophilus gallinarum* developed. At the 1954 Antibiotic Conference, Hawley et al.[284] stated that none of the organisms cultured from refractory mastitis infections were truly resistant to all antibiotics.

(To be continued)

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MEDICAL INTELLIGENCE

TRANSMISSION OF INFECTIOUS HEPATITIS BY TRANSFUSION OF WHOLE BLOOD*

With a Note on the Early Appearance of Viremia in this Disease

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CLINICAL, epidemiologic and experimental studies in recent years have defined some of the features of infection with the viruses of infectious (epidemic) hepatitis and serum hepatitis. It has been noted that the former disease is usually transmitted by person-to-person contact, probably by the fecal-oral route; the virus of infectious hepatitis has been found in the stool in acute cases of the disease,[1,2] and in the stools of 2 children, five and fifteen months respectively after the acute illness.[3]

Blood-stream invasion by this virus is probably common, and may be an integral part of the infection; it has been noted in the acute phase of the disease and as early as three days before the onset of symptoms.[1-5] The earliest documented viremia to date occurred thirteen days before the appearance of jaundice.[6]

Although infectious hepatitis can be passed experimentally in human subjects, by means of acute-stage whole blood as the inoculum, by the oral or parenteral routes,[1,2,5-7] this mode of infection is exceedingly rare under ordinary clinical conditions. The following clinical and epidemiologic observations are reported because they suggest that under nonexperimental conditions infectious hepatitis was transmitted from person to person by transfusion of infectious blood, rather than by the usual fecal-oral route. Furthermore, the data demonstrate that viremia may appear earlier in the course of this infection than has previously been recognized.

CASE REPORTS

CASE 1. A 23-year-old graduate nurse donated blood to the hospital blood bank on March 10, 1954. Eleven days later coryza developed and was followed in 3 days by anorexia, nausea, vomiting and abdominal pain of mild degree. Twenty-three days after the blood donation she noted pale stools and dark urine, and 2 days later she became icteric. Physical examination revealed a temperature of 100.4°F. by rectum, mild jaundice, tender hepatomegaly and abdominal distention. Urine tests for bile were strongly positive, and a 2-hour specimen contained 3.6 Ehrlich units of urobilinogen. The serum alkaline phosphatase was 11.7 Bodansky units, and the total serum bilirubin was 4.9 mg. per 100 cc. (3.1 mg. direct and 1.8 mg. indirect). Thymol turbidity was 3 units, cephalin-cholesterol flocculation 10 units, and serum cholesterol 161 mg. per 100 cc., with 49 per cent esters. On bed rest and dietotherapy the symptoms and signs rapidly subsided, and she was discharged from the hospital 20 days after admission. The final clinical diagnosis was infectious hepatitis.

CASE 2. A 40-year-old housewife had a radical mastectomy for carcinoma of the breast. She gave no past history of jaundice or known biliary-tract disease, and had had no injections in the past. Before operation the liver and spleen were not palpable, and chemical studies revealed a serum alkaline phosphatase of 1.7 Bodansky units on 1 occasion and 1.5 Bodansky units on another; the total serum protein was 7.1 gm. per 100 cc., with an albumin of 4.5 and a globulin of 2.6 gm. per 100 cc.

At operation on March 15, 1954, she received 2 transfusions of whole blood of 500 cc. each. She did well postoperatively and was discharged from the hospital on March 27.

Fourteen days after the transfusions a pruritic maculopapular eruption on the lower extremities, associated with anorexia, lethargy and headache developed; 13 days later she noted dark urine and chilly sensations and was nauseated. On the 30th day after the transfusions she became jaundiced and was readmitted to the hospital.

Physical examination revealed a temperature of 100.2°F. by rectum, with hepatosplenomegaly. An x-ray film of the chest was normal. The white-cell count was 10,500, with a normal differential. Urine tests for bile were positive, and a 2-hour specimen contained 4.4 Ehrlich units of urobilinogen. The total serum bilirubin was 10.8 mg. per 100 cc. (7.6 mg. direct and 3.2 mg. indirect). The thymol turbidity was 17 units; a bromsulfalein test showed 32.7 per cent retention of the dye in 45 minutes (5 mg. per kilogram injected). The serum cholesterol was 326 mg. per 100 cc., with 11 per cent esters. The serum alkaline phosphatase was 5.3 Bodansky units; the total serum protein was 7.7 gm. per 100 cc., with an albumin of 3.9 and a globulin of 3.8 gm. per 100 cc.

On bed rest and dietotherapy the symptoms and signs subsided fairly rapidly, and the patient was discharged on the 38th hospital day, when the total serum bilirubin was 0.5 mg., the serum cholesterol 395 mg. (with 65.8 per cent esters), and the total serum protein 7.2 gm. per 100 cc., with an albumin of 4.4 and a globulin of 2.8 gm. per 100 cc. The final clinical diagnosis was viral hepatitis, possibly serum hepatitis.

The blood given in Case 2 was traced. One unit (500 cc.) had been donated to the hospital blood bank six days before transfusion by a forty-year-old man who was not a professional donor. He gave no history of jaundice or of known hepatobiliary disease, and had received no injections for many years. Physical examination at the time of his blood donation was negative. When seen three months after the donation he was in good health, and physical examination was again negative. The serum bilirubin, alkaline phosphatase and total protein (with albumin and globulin) were normal.

The second unit (500 cc.) of blood given in Case 2 was the one donated by Case 1 eleven days before the onset of her illness and twenty-five days before she became jaundiced. The time relations are summarized in Table 1.

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Discussion

The situation described above is thought to represent transmission of viral hepatitis from Case 1 to Case 2. It is our belief that the virus of infectious hepatitis rather than that of serum hepatitis was involved. These conclusions have been reached for the following reasons:

Table 1. *Time Relations in the Transmission of Infectious Hepatitis by Transfusion of Whole Blood.*

Date	Event
1954	
March 10	Blood donation by Case 1
March 15	Case 2 received transfusion
March 21	Onset of illness in Case 1
March 29	Onset of illness in Case 2*
April 4	Onset of jaundice in Case 1
April 15	Onset of jaundice in Case 2

*Incubation period, 14 days.

Case 1 was a nurse working in a pediatric outpatient facility through which children with a variety of infectious and noninfectious diseases pass. Her duties included taking rectal temperatures on these patients and occasionally bleeding them for laboratory examinations. Although specific contacts with patients with infectious hepatitis were not recalled, such contacts are not a necessary part of the epidemiologic evidence that her illness may have had its source in her work in the pediatric clinic. This is so because infectious hepatitis is frequently a mild, atypical and anicteric disease, especially in children,[8] so that exposure to active cases may not be recognized.

Case 1 had had no transfusions at any time. She had had no immunizations or other injections for twelve months before the onset of her illness. Since incubation periods of twelve months have not been noted with either infectious or serum hepatitis, these injections appear to bear no relation to the illness described in this patient.

Case 2 had had no known exposures to patients with viral hepatitis before the onset of her illness. There had been no known exposure to hepatotoxins, and she had received no injections before the first hospitalization described above. Although she had received one other transfusion of whole blood at the same time as that from Case 1, the donor involved presented no history or physical or chemical evidence of viral hepatitis at the time of the blood donation, and no evidence that he had had it before that time.

The possibility that this donor was an asymptomatic carrier of infectious hepatitis virus cannot definitely be ruled out, nor can the possibility that Case 2 had contracted sporadically occurring infectious hepatitis unrelated to either of her transfusions. However, since she had received a transfusion of blood from a patient with known viral hepatitis shortly before its onset, and because viremia appears to be a common accompaniment, if not an integral part of these infections, it seems far more reasonable to conclude that her disease was related to the transfusion received from Case 1.

The interval between transfusion and onset of illness in Case 2 was fourteen days. Both this interval and that between transfusion and the appearance of jaundice (thirty days) are shorter than the incubation periods of serum hepatitis reported from clinical practice and from experiments in human volunteers.[9] Both intervals, however, are well within the range of incubation periods described for infectious hepatitis.[9] Finally, gamma globulin may offer protection against viral hepatitis, and might therefore prevent post-transfusion infection.[10]

Summary and Conclusions

An instance of apparent transmission of infectious hepatitis by transfusion of infectious blood is reported. This situation is thought to be of unusual interest because it provides evidence that the virus of infectious hepatitis may appear in the blood as long as eleven days before the onset of symptoms and twenty-five days before the appearance of jaundice. Also, it points up the fact that, under nonexperimental conditions, infectious hepatitis may be transmitted from person to person by a route other than the usual fecal-oral one, — that is, by transfusion of infectious blood.

This situation suggests that data on the incidence of serum hepatitis after transfusion with whole blood should be interpreted with caution, since some of the cases of viral hepatitis that follow transfusions may in actuality represent infection with the virus of infectious hepatitis rather than with the virus of serum hepatitis.

Finally, this experience suggests that some cases of post-transfusion hepatitis — that is, those due to the virus of infectious hepatitis — might be preventable through the use of human serum gamma globulin, since this material protects exposed susceptible persons against infection with this virus, even though such protection is apparently not afforded for serum hepatitis.

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BY THE LONDON POST

The Doctor and the Law — Noise in Hospitals

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THE large number of legal actions brought against physicians and surgeons is still causing concern. A new feature of the annual report of the Ministry of Health is the inclusion of tables to show the frequency of claims and proceedings against hospitals and their medical staffs. These demonstrate that compensation payments of all kinds, largely in negligence cases, rose from £23,636 in 1950 to £159,047 in 1953. In his report, the president of the Medical Defence Union has said that the number of claims for alleged medical negligence was 80 per cent higher in 1953 than in 1947. The report of the Ministry of Health states that there is no evidence of deterioration in the standard of medical practice and attributes the increased litigation to a number of factors. Perhaps the most important of these is the decision in several recent court cases that, under the law, the hospital is responsible for the negligence of its servants. In the days of voluntary hospitals, there was a great loyalty to the local hospital and its staff, and this acted as a forceful deterrent to persons who might otherwise have considered taking legal action. Now that the local hospital is no longer "our hospital" but just a part of the National Health Service, proceedings are taken against it without any personal feelings whatever. Another factor that has doubtless contributed to the increase in the number of actions and has been responsible for a number of the frivolous ones is the provision of free legal aid.

The effect on the medical staff is serious. The young resident is often unwilling to undertake the responsibility of a casualty department because he is only too well aware of the pitfalls and dangers; the surgeon may sometimes be loath to undertake the risky case, and the outpatient physician finds himself ordering large numbers of investigations chiefly with a view to excluding organic disease to safeguard himself and the patient's general practitioner against missing a diagnosis and exposing themselves to a charge of negligence.

It must be remembered, however, that a plaintiff cannot win his case on a medical mistake, but has to prove negligence in the strict legal sense. To help reduce the frequency of litigation the president of the Medical Defence Union has emphasized a number of points. First of all, he has stressed the importance of keeping the patient and his relatives informed about his illness and its treatment. In a hospital the patient enters a foreign world, where the language spoken around him is often incomprehensible. He may not even be told what is wrong with him or what the surgeons and physicians intend to do or have done. In particular, he may not be told of a complication in his case. It may frequently be desirable to withhold certain information on the grounds that it would cause anxiety that would be harmful. On the other hand, when it is learned in a court of law that the full facts of a case have not been disclosed, the goodwill extended to a medical defendant may be withdrawn. It is therefore desirable that if on medical grounds it is necessary to withhold certain facts from the patient, a responsible relative should be kept fully informed about the progress of the case.

The other point stressed is the importance of keeping good clinical notes. Many a case has been imperiled by the fact that the notes do not tally with the evidence given by the doctor in the witness box. Good case notes taken at the time can be of the greatest value in supporting a practitioner's version of the facts against the version of the patient and his relatives.

The best insurance, therefore, against unjustified legal action is the maintenance of a high standard of medical practice and the continued fostering of a satisfactory doctor-patient relation. This is, of course, a two-sided affair demanding confidence on the part of the patient and conscientious good faith on the part of the practitioner. If either side of the relation breaks down, the results are bound to be detrimental to the patient and may lead to the kind of situation from which legal action results.

* * * *

Complaints about noise in hospitals continue to be made and it is now generally accepted that this is a serious problem. The principal reasons for the present noisy conditions are known. There is more nursing and medical activity, with more walking, more transport, especially by trolley, more mechanical equipment and more sanitary fittings. Compact planning has brought the sources of noise nearer to the patient, and the lighter panel walls and partitions of modern framed structures are less resistant to sound than the heavier, solid masonry walls used in the past.

A recent survey into the actual cause of ward noises revealed that much of it originates in corridors. The principal causes of noises in daytime appeared to be trolleys and the slamming of doors. It seems almost unbelievable that in one ward, between 9 and 10

a.m., 300 door slams were recorded. The nonabsorbent finishes in the corridors increase reverberation and prevent noise from dying away. The average night levels were attributed to mechanical noises such as running machinery and water or steam pipes. Sanitary appliances, particularly water closets and bed-pan washers, are also responsible for considerable ward noise because both are often situated close to the actual bed areas in wards.

Among the many factors that affect the toleration of noise in hospital wards are the patients' normal tolerance of noise, the nature of their illnesses and the state of convalescence that they have reached. One can control sound by minimizing noise at its source, by providing sound-reducing walls and floors and by applying absorbents to surfaces where noise is likely to occur. Silently closing doors, fiber runners to bed curtains and cork floor finish are all measures that will reduce noise at its source. The provision of a central sterilizing room for the hospital reduces the amount of sterilizing of equipment that normally takes place within the ward unit and is a further way of eliminating noise at source.

It has been suggested that an essential part of a young doctor's training should be a period as a patient in his own wards. Only then would he realize the importance of quiet in the healing process. Indeed, the whole of the team in a modern hospital should be drilled in the idea that rest and quiet have themselves a high reputation as healing measures.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41471

PRESENTATION OF CASE

A fifty-three-year-old man entered the hospital because of enlargement of a hernia and shortness of breath.

Three years before admission the patient felt "something give" in his right groin as he lifted a box. Thereafter a swelling developed, and he began to wear a brace. One year before entry a firm mass became palpable in the scrotum. This was thought by the patient to be part of the hernia, which was gradually increasing in size. For two years he had no libido and was impotent. Six months before admission marked the onset of dyspnea on exertion; thereafter, orthopnea and ankle edema developed.

A son returned home from a tuberculosis sanatorium just before his father's admission. The patient smoked 2 packages of cigarettes a day. For twenty-five or thirty years he had drunk considerable wine and eaten poorly.

Physical examination revealed a slender, smooth-skinned man showing some wasting of subcutaneous tissue and muscles. There was a right inguinal hernia. The scrotum contained loops of bowel and below them a grapefruit-sized, stony-hard, nontender

FIGURE 1.

mass, which did not transilluminate. The left testis felt atrophic. There was bilateral enlargement of the breasts, with apparent increase in glandular tissue and hyperpigmentation of the areolae (Fig. 1). Axil-

lary hair was sparse and hair on the lower abdomen had a female distribution. The neck veins were distended and pulsating when the patient was raised to 30°. The heart was enlarged. A Grade 4 high-pitched systolic murmur accompanied by a thrill was heard over the precordium. The lungs were clear to percussion and auscultation. A firm smooth tender liver edge was palpable 2 fingerbreadths below the right costal margin. There was +++ ankle edema. The prostate was of normal size or even slightly atrophic.

The temperaure was 99.8°F., the pulse 90, and the respirations 20. The blood pressure was 200 systolic, 140 diastolic.

Urinalysis was negative. Initial examination of the blood revealed a hemoglobin of 17.5 gm. per 100 cc. and a hematocrit of 56 per cent. The white-cell count was 9200, with a normal differential. The nonprotein nitrogen was 32 mg., the fasting blood sugar 90 mg., the calcium 9.4 mg., the phosphorus 3.0 mg., the bilirubin 1.1 mg., and the cholesterol 247 mg.; the potassium was 4.3 milliequiv., the sodium 138 milliequiv., the chloride 106 milliequiv., and the carbon dioxide 26 milliequiv. per liter. The prothrombin time was 14 seconds (normal, 13 seconds). The alkaline phosphatase was 4 Bodansky units, and the acid phosphatase 0.1 units prostatic (normal, under 0.6 units) and 0.7 units total per 100 cc. Bromsulfalein retention was 7 per cent in forty-five minutes. A blood Hinton test was negative. The basal metabolic rate was +17 and +34 per cent on two occasions. The protein-bound iodine was 10.7 gamma per 100 cc. A glucose tolerance test was normal. An eosinophil count was 143 per cubic millimeter. Two hours after the start of an eight-hour intravenous infusion of 25 mg. of ACTH the eosinophil count was 90 per cubic millimeter; at four hours it was 19 per cubic millimeter. Nine determinations of urinary 17-ketosteroid excretion before ACTH administration gave values ranging from 4.6 to 9.5 mg. and averaging 6.1 mg. per twenty-four hours. After ACTH administration the 17-ketosteroid level rose to 16.1 mg. per twenty-four hours, both on the day of infusion and on the next day. On the fourth day after ACTH, the 17-ketosteroid level fell to 8.8 mg. per twenty-four hours. Two Silber–Porter determinations of corticoids showed an average value of 4.5 mg. per twenty-four hours. After ACTH administration the level increased on the same day to 9.2 mg. per twenty-four hours. Estrogen excretion measured as fluorogenic phenols by sulfuric acid fluorescence was approximately twice the normal amount. An FSH (follicle-stimulating-hormone) test was negative for 6.5, 13 and 52 mouse units per twenty-four hours. Injection of an aqueous extract of a 95 per cent alcohol protein precipitate of urine elicited no ovarian response in immature female mice.

An electrocardiogram was interpreted as showing atrial hypertrophy and an old septal infarct. An x-ray film of the chest revealed an area of increased density, 1.5 cm. in diameter, in the right-upper-lung field and cardiac enlargement. A second film four weeks later showed no change in the pulmonary lesion. Films of the kidneys, bladder, dorsal and lumbar spine and skull and an intravenous pyelogram were normal. A barium-enema examination revealed terminal ileum in the scrotum, but was otherwise negative. An x-ray film of the scrotum disclosed one small area of calcification.

The patient was treated for the cardiac condition. On the seventeenth hospital day an operation was performed.

Differential Diagnosis

Dr. Henry M. Lemon*: Two chief complaints —enlargement of a hernia associated with a grapefruit-sized mass and shortness of breath, probably associated with ankle edema—indicate two major disorders. We teach our students that a hernia that develops in the middle years of life or later may be the result of an exacerbation of a cough, which in turn may be the result of a benign disease or even carcinoma of the lung. That, however, would not explain the mass in the scrotum, which apparently developed coincidentally with the hernia.

For two years this man had had no libido and was impotent. I find this difficult to interpret in spite of all the drug literature on the virtues of testosterone and other hormones. He probably had had considerable nutritional deficiency and a considerable ethanol intake, which of course may have contributed to these symptoms.

Some of the most valuable clues were given in the physical examination. The mass on the right had all the characteristics of a tumor, in that it was stony hard, did not transilluminate, had been increasing in size and showed some calcium on x-ray examination.

There was atrophy of the left testis along with bilateral gynecomastia and hyperpigmentation of the areolae. Gynecomastia may develop in patients with hepatic cirrhosis, probably as a result of decreased hepatic inactivation of estrogens. Moreover, we have occasionally seen cases of gynecomastia that developed one to three years before discovery of bronchogenic carcinoma or some other malignant tumor. Gynecomastia is difficult to interpret etiologically since both androgen and estrogen therapy as well as the spontaneous endocrine changes associated with nutritional repletion after prolonged malnutrition—such as occurred in American prisoners of war in the Philippines—may produce it. There are other evidences of endocrine imbalance also. The axillary

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hair was sparse, and there was a female distribution of the hair on the abdomen.

On physical examination this man also had evidence of cardiac enlargement and a high-pitched systolic murmur. In view of the electrocardiogram interpreted as indicating a septal infarct, the loudness of the murmur and thrill makes one wonder about the possibility of a septal perforation, but I doubt that this man would have waited for such a long period before coming into the hospital with a septal perforation unless it was a very small one. Ordinarily, with a septal perforation, a very loud machinery type of murmur is heard both in systole and in diastole. This could also, of course, greatly increase the venous pressure.

The ankle edema is consistent with the other evidence of congestive heart failure, but in view of the scrotal tumor I must also consider the possibility that enlarged retroperitoneal lymph nodes caused venous obstruction that resulted in ankle edema.

The prostate was of normal size or even slightly atrophic. There were probably several observers. I prefer to believe that it was of normal size. So much of the prostate consists of fibrous tissue that the glandular epithelium would have to be exceedingly atrophic to produce a marked decrease in size.

This man had considerable hypertension and an impressive polycythemia. Immediately, these raise the question of endocrine changes. The polycythemia was not apparently a polycythemia rubra vera, for the white-cell count was normal, with a normal differential. The polycythemia may have been associated with prolonged congestive heart failure and chronic anoxia; on the other hand it may have accompanied the hypertension, and may have indicated adrenal hyperactivity, possibly Cushing's syndrome or a considerable increase in the secretion of the androgenic steroids. We know that some women who receive testosterone therapy exhibit a considerable increase in the red-cell count and hematocrit. I cannot explain the hypertension on the basis of renal disease because urinalysis was negative and the nonprotein nitrogen was normal. Adrenocortical dysfunction is not indicated by the electrolytes, which were within normal limits except for a slightly low carbon dioxide. The prothrombin time and liver-function tests do not impress me as indicating a severe degree of liver disease. There was no mention of ascites or of values for plasma protein. I cannot interpret the gynecomastia on the basis of severe liver disease. Ordinarily, patients with hepatic cirrhosis who have feminizing manifestations, have spider telangiectases, ascites and a much more reduced liver function than this patient had.

The basal metabolic rate was elevated. I do not know what this means in a man with heart failure, with the possibility of a malignant tumor and with dyspnea. The protein-bound iodine was somewhat elevated. There was no mention of thyroid enlargement; I cannot be sure that he had not been exposed to iodide-containing medications at some time in the past. The glucose tolerance test was normal. The eosinophil count was within the normal range; the eosinophils responded normally to intravenous infusion of ACTH. The 17-ketosteroids were within the range that one would expect in a man who had a systemic disorder. Certainly, patients with liver disease or congestive heart failure manifest low 17-ketosteroids as a result of their intercurrent diseases. It would be well to mention that the 17-ketosteroids determination is merely a colorimetric assay and that the various steroids differ considerably in their chromogenic value, as pointed out in several laboratories. That is another factor to confuse the poor clinician who tries to make use of the determinations. That the 17-ketosteroid level responded adequately to ACTH and fell promptly to a normal range indicates that the patient had responsive adrenal glands. The urinary corticoids were within normal limits; this does not help me make a diagnosis of a hyperfunctioning adrenal tumor. I mention this possibility because from time to time adrenal rests in the location of the testis have become neoplastic; sex hormones, including estrogens, have been isolated from such tumors.[1]

The twofold increase in the urinary estrogen excretion is quite consistent with the other findings and would account for many of the physical findings. Apparently, no chorionic type or follicle-stimulating type of gonadotropin was identified in the urine of this patient. In the literature frequently, but by no means always, an increased gonadotropin titer has been reported in males with testicular tumors and gynecomastia, but the exact type of gonadotropin present is not always clearly stated. With embryonal carcinomas, choriocarcinomas and some of the teratocarcinomas a chorionic type of gonadotropin is found. In the cases of the seminomas, which are more common in men of this age group, the follicle-stimulating hormone is often elevated to a higher level than is usual in an elderly male. It is certainly unusual not to find any follicle-stimulating hormone in the urine in the absence of any other sign of pituitary insufficiency. Therefore, I should be more inclined to believe that the estrogen production from some locus in the body of this patient was such as to inhibit completely the normal production of pituitary follicle-stimulating hormone rather than that a diffuse disease of the pituitary gland was responsible for the absence of this hormone. Estrogens are considerably more potent as inhibitors of pituitary follicle-stimulating hormone than androgens—such as testosterone.

The electrocardiogram indicated heart disease, which I am going to pass over. A density in the right-upper-lung field was noted in the roentgenograms. May I see the films?

DR. JOSEPH HANELIN: There is a 1.5-cm. nodule, which lies either in the dorsal segment of the right lower lobe or in the posterior segment of the upper lobe close to the septum. This has not changed in size in films taken two months later; the heart, however, appears to have enlarged in that interval, and the pulmonary vessels may be slightly more engorged. The cardiac enlargement is chiefly left ventricular. The scrotum contains gas-filled loops of bowel and a large homogeneous mass within which is a small, round, fairly smooth, calcific fleck. The other examinations are negative.

DR. LEMON: It is probably presumptuous on the basis of the information that I have on this patient to try to make a histologic diagnosis of the mass in the right testis; however, I shall try. Among the tumors that arise from the differentiated elements of the testis are Leydig-cell tumors. These are rare, are usually masculinizing and may produce precocious puberty. I think, however, that on occasion they may be associated with hyperestrinism. Seminomas are believed to arise from the spermatogonia of the seminiferous tubules. These tumors frequently are not pure seminomas, but may be mixed with other elements. As a rule they do not produce striking endocrinologic manifestations, such as gynecomastia and elevated sex-hormone excretion. They tend to be less malignant than the teratomatous tumors and to metastasize by the lymphatics to the retroperitoneal lymph nodes. They would not be so likely to produce a mass in the lung field. The classic pulmonary coin lesion that this patient had may have been a tuberculoma, or a hamartoma or some benign tumor, but statistically about a third of such lesions are malignant tumors—frequently solitary metastases. Such a metastasis would be typical of the more undifferentiated testicular tumor.

Tumors derived from primitive germ cells consist first of the trophoblastic tumors, such as the embryonal carcinomas and the chorionepitheliomas. The chorionic type of gonadotropin is usually found in the urine of a patient with a primitive germ-cell tumor of this size and with possible metastases. The second type of tumors from primitive germ cells, the somatic tumors, include the teratocarcinomas and teratomas, which are less likely to produce augmented estrin excretion. We have evidence, on the basis of the study of at least one embryonal carcinoma carried out by our laboratory,[2] that the embryonal type of testicular tumor can synthesize in vitro from 1-C-14 acetate, testosterone, delta-4 androstene dione, progesterone, estrone and estradiol. These studies were carried out in the presence of chorionic gonadotropin (antuitrin S), and I believe that they indicate that an embryonal tumor may synthesize enough estrogen to counterbalance whatever residual androgens may be synthesized.

I believe that the patient under discussion had a malignant tumor of the testis, most probably an embryonal type of carcinoma without a striking preponderance of trophoblastic elements, and that he probably had pulmonary metastases. With that type of tumor I should not anticipate much gonadotropin excretion, as a result of pituitary inhibition by estrogens produced by the tumor. I could find in the literature no mention that in these tumors, at least in the teratocarcinomas, thyroid tissue occurs, which might account for an elevated protein-bound iodine. I believe that the other manifestations, the polycythemia and so forth, were secondary to hypertensive cardiovascular disease, perhaps with an old infarct and with congestive heart failure, which I assume responded to therapy. It is possible, however, that the patient had an adrenal rest, with a very unusual tumor, which was producing some steroid other than estrogens.

A PHYSICIAN: I want to ask whether the protein-bound iodine was determined before or after the intravenous pyelogram.

DR. WILLIAM H. BAKER: We interpreted the elevation as due to the intravenous pyelogram, which was taken a week before the iodine determination.

I think that Dr. Lemon has given us an excellent discussion of this case. We thought along similar lines. In view of the round lesion in the chest we believed that this patient had a malignant tumor of the testis. On the evidence of the gynecomastia, the pigmentation of the areolae, the increase in the fluorogenic phenols, the perhaps slight decrease in the size of the prostate, the decreased libido and the impotence, we believed that this man had an estrogen-producing tumor of the testis, probably malignant. Our preoperative diagnosis was a malignant tubular adenoma or Sertoli-cell tumor, with metastasis to the lung.

CLINICAL DIAGNOSIS

Malignant tubular adenoma, (Sertoli-cell tumor) of testis, with metastasis to lung.

DR. HENRY M. LEMON'S DIAGNOSIS

Embryonal carcinoma of testis, with metastasis to lung.

ANATOMICAL DIAGNOSES

Granulosa-cell tumor of testis.
Testicular atrophy, bilateral.
Gynecomastia.

PATHOLOGICAL DISCUSSION

DR. ROBERT E. SCULLY: We selected this case for clinicopathological conference because it represented an interesting and complicated endocrinologic problem. I think the exact diagnosis is as nearly impossible to make clinically as in any case I have ever seen, because I believe it is the first one of its kind.

The mass removed at operation was a solid testicular tumor weighing approximately 1000 gm. On section nodular yellow tissue separated by bands of fibrous tissue showed focal areas of necrosis and hemorrhage (Fig. 2). This is a very unusual appearance for a testicular tumor; the yellowish color, of course, suggests the presence of some endocrine-producing tissue. On microscopical examination, we were surprised to find a typical granulosa-cell tumor of the kind that we are accustomed to see in the ovary. The tumor cells were growing diffusely, and their nuclei had a characteristic windblown appearance, with their long axes oriented in diverse directions (Fig. 3). Under high power many of the nuclei had longitudinal grooves, another feature of granulosa-cell tumors in the ovary. The only alternative diagnosis we considered was Sertoli-cell tumor. This is an extremely rare tumor in the human testis, but is a comparatively common cause of feminization in dogs. However, in a series of some 30 Sertoli-cell tumors in dogs,[2] we have never seen one resembling the tumor in this patient. When we concluded that this was a granulosa-cell tumor, we wondered whether it might be arising in an ovary instead of a testis. This seemed unlikely, for the patient gave no other evidence of true hermaphroditism. We took multiple sections of the capsule of the tumor and found only testicular tissue composed of compressed atrophic tubules. We examined a biopsy specimen of the opposite gonad taken somewhat later. This again showed atrophic testis with some cells of the spermatogenic series remaining in the tubules and typical Leydig cells. We further examined a skin biopsy, which we believed showed the chromatin pattern of a male. As far as we know, this is the only existent granulosa-cell tumor of the testis with clear-cut evidence of hormonal function.

FIGURE 2.

Dr. Baker, will you tell us something of the follow-up course of this patient?

DR. BAKER: This man had an uneventful postoperative course. We have followed him for several months postoperatively. The left testicle is no longer atrophied; his libido has returned; he is no longer impotent; and he is having sexual intercourse once or twice a week. The gynecomastia has disappeared, although the pigmentation of the areolae is still present.

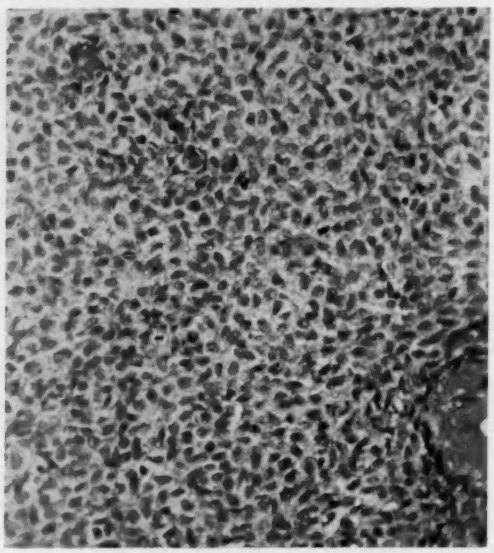

FIGURE 3.

DR. BENJAMIN CASTLEMAN: Dr. Scully, do you think that this was a benign tumor and that the lesion in the lung is not a metastasis?

DR. SCULLY: I think that metastasis is possible but highly improbable, judging from the behavior of granulosa-cell tumors in the female.

DR. HANELIN: A film of the chest taken three months later shows the lesion to be exactly the same.

It is probably a benign lesion, such as a hamartoma or tuberculoma.

DR. ANNE P. FORBES: Did the FSH revert to normal?

DR. BAKER: I am afraid that the last urine sample for FSH assay was broken in transit.

DR. FORBES: If the patient had one normal FSH level postoperatively, one might be advised of a recurrence if and when the FSH dropped again.

DR. BAKER: We have some steroid studies on him on which Dr. Baggett might like to comment.

DR. BILLY BAGGETT: Before operation the total estrogens appeared to be slightly elevated—90 microgm. per twenty-four hours. After removal of the tumor, however, the drop was not striking, the value being about 70 microgm. A pooled preoperative urine sample was taken, and this was investigated by countercurrent distribution of the estrogens. The patient was excreting 13 microgm. of estrone, and 7.5 microgm. of estriol per day before operation. After the operation, there were still recognizable estrogens but at a lower level; the level of estrone had fallen to about 7 microgm., and that of the estriol to 6 microgm., which was essentially the same as before removal of the tumor. Other studies showed that the ketosteroids did not change after operation. The corticoids remained the same, with the exception of a slight rise immediately after operation. We also extracted the tumor itself and analyzed the extract; we found no sign of estrogens in the tumor. We are now in the process of incubating the tumor with C-14 acetate and with labeled testosterone in the hope of finding out whether any estrogen is produced from these precursors.

DR. SCULLY: Dr. Cohen has some interesting histochemical findings on the tumor tissue.

DR. RICHARD B. COHEN: Most areas of the tumor studied histochemically contained no lipid material. Patchy areas showed Sudan-IV-positive droplets both in the cytoplasm of the cells and extracellularly. This lipid did not, however, react with reagents for the demonstration of cholesterol, ketonic or aldehydic carbonyl groups as phospholipids. This lipid pattern differs from the usual one found in steroid-hormone-producing glands such as the adrenal cortex. These negative histochemical findings and even the negative quantitative results do not exclude the production of estrogens by this tumor since both methods neglect the important factor of turnover rate.

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CASE 41472

PRESENTATION OF CASE

A fifty-two-year-old man entered the hospital because of hoarseness.

The patient was in excellent health until three months before admission, when he began to feel "run down," weak and anorectic. Over the next two and a half months he lost approximately 10 pounds of weight. One month before entry he noticed the onset of a hacking cough productive of small amounts of nonbloody sputum. This was followed by the gradual appearance of hoarseness, which progressively

FIGURE 1. *Posteroanterior View of the Chest. Arrows indicate the small mass in the left side of the mediastinum at the level of the proximal aortic arch.*

increased up to the time of admission. An examination of the larynx done in the Clinic revealed paralysis and fixation of the left vocal cord. A lateral x-ray film of the neck was normal. The patient was referred to the hospital for further study.

The past history was noncontributory. There was no difficulty in swallowing and no dyspnea, hemoptysis or pain in the chest. The patient had smoked one or two packages of cigarettes every day for many years.

Physical examination revealed a well developed man with evidence of recent weight loss. The voice was hoarse and rasping. The neck was normal. The chest was resonant, with a harsh late inspiratory wheeze in the right side. The heart was normal, as

was the abdomen. There was marked clubbing of the finger and toenails and no cyanosis.

The temperature was 97°F., the pulse 76, and the respirations 18. The blood pressure was 160 systolic, 85 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 12.2 gm. per 100 cc. and a white-cell count of 8400. A blood Hinton test was negative. The albumin and globulin were normal, and liver-function tests were negative. An electrocardiogram was within normal limits.

An x-ray film of the chest showed a round mass protruding into the left-lung field just below the aortic arch (Fig. 1). The mass appeared to lie in the anterior mediastinum and showed slight pulsations. The lungs were emphysematous, with depression and

FIGURE 2. *Lateral View of the Chest.*
Arrows indicate the small mass in the mediastinum at the level of the proximal aortic arch.

flattening of the diaphragm. The leaves of the diaphragm moved equally bilaterally. The anteroposterior diameter of the chest was increased. There was no mediastinal shift. The heart showed prominence of the left ventricle and the aortic arch. Fluoroscopy of the chest with multiple views of the lung fields showed no other masses. The mass previously described moved with the aortic arch in a manner suggesting that it was fixed to it. An angiocardiogram revealed that the mass stated to be in the region of the left ductus node did not opacify as the dye went through the pulmonary vascular circuit and the aorta. The left-upper-lobe pulmonary artery was pressed upon by the mass, and there appeared to be some irregularity of the left upper posterior apical pulmonary artery, suggesting the possibility of attachment to the vessel wall. In the later films there appeared to be a compression upon the left lateral inferior aspect of the aortic arch by the mass (Fig. 2).

Bronchoscopy revealed paralysis of the left vocal cord and questionable slight deviation of the trachea to the right. The right and left main bronchi and their lobar branches appeared normal. Bronchoscopic washings from the left main bronchus were negative for tumor cells.

On the thirteenth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. HELEN S. PITTMAN*: The differential diagnosis of an anterior mediastinal mass is a guessing game at best, but a guessing game based on certain standard principles. The patient's illness began with weight loss, which is a general manifestation of disease. He had a cough, which is evidence of pressure, and hoarseness and paralysis of the left vocal cord, which suggest involvement of the left recurrent laryngeal nerve. In view of the negative bronchoscopy, I think the wheeze heard in the right side of the chest was not related to the mass but rather to emphysema. May we look at the x-ray films now? I understand that the angiocardiogram cannot be demonstrated, for it is a long roll that requires four people to hold.

DR. C. C. WANG: The x-ray films of the chest taken on admission show a soft-tissue density projecting into the left-midlung field (Fig. 1). It lies somewhat below the aortic knob and apparently above the left main bronchus. There is no unusual calcification within it. On the lateral film this density lies somewhat anteriorly and has a very sharp border (Fig. 2). On fluoroscopy it appeared to follow the aorta and could not be separated from it. The diaphragm moved well bilaterally. The heart is not enlarged, and the aorta shows some calcification in its arch. The lung fields are clear otherwise.

DR. PITTMAN: Do you know whether the pulsation in the mass was transmitted or intrinsic?

DR. WANG: Dr. Reeves fluoroscoped the patient; perhaps he can answer that.

DR. JOHN D. REEVES: The mass did not pulsate intrinsically but by transmission.

DR. PITTMAN: Dr. Wang, do you suspect from the angiograms that this was a vascular lesion? Was an aberrant vessel demonstrated? What was the relation of the visualized vessels to the mass?

DR. WANG: The mass appeared to displace the vessels in the left upper pole, but was not opacified by the contrast medium.

DR. PITTMAN: Is there any suggestion of peripheral shadows in either lung?

DR. WANG: No; the peripheral lung fields are clear.

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DR. PITTMAN: Is the mucosa of the esophagus normal in the barium-swallow examination?

DR. WANG: Yes; there is no intrinsic involvement of the esophagus.

DR. PITTMAN: I come down to the diagnosis of an anterior mediastinal mass situated below the aortic arch confined to the left side, and transmitting pulsation. It involved the left recurrent laryngeal nerve and was probably fixed to the arch of the aorta. It was in the region of the left ductus node and may have impinged on the artery to the left upper lobe. It seems to me that given that set of circumstances the field of discussion narrows to either a vascular lesion or a malignant neoplasm. Involvement of the nerve in benign or inflammatory lesions is so rare as hardly to warrant consideration. First about vascular lesions, one has to consider aneurysms of the aorta. An aneurysm of the transverse aorta may involve the left recurrent laryngeal nerve, but this usually gives dysphagia as well as cough. This man had no difficulty swallowing. There are rare cases of aneurysm on the concave side of the ascending aorta that may appear anteriorly and to the left of the sternum in contrast to the usual position. However, if this mass did not opacify on the angiogram, I have to say that it was not an aneurysm. Moreover, an aneurysm would not explain the marked clubbing without cyanosis.

That brings me to malignant neoplasm. The fact that this man had severe clubbing and nerve paralysis is strong evidence in favor of this diagnosis. Starting with the primary tumors, I believe the mass was not a primary bronchogenic carcinoma in spite of the history of heavy smoking. In view of the negative bronchoscopy and cytologic examination in the presence of a central lesion there is no logical reason for making that diagnosis.

Lymphoma occurs in the mediastinum and is always a good guess when one does not know what the lesion is. Lymphoma, however, is more likely to be bilateral, although it can be localized to one side. This man had no recorded fever and no other enlarged lymph nodes so there is nothing on which one can make a reasonable diagnosis of lymphoma.

Coming to the other structures that occupy the mediastinum, I think one must consider a primary lesion in the esophagus. Although the esophagus comes in close contact with the aortic arch and left main bronchus, I do not see how I can make a diagnosis of a mass arising in the esophagus, when there is no dysphagia, no pain and an apparently intact mucosa.

Thymic tumor and teratoma both occur in the anterior mediastinum; it is always anyone's guess whether or not one of those is present.

I do not know enough about primary blood-vessel tumors to discuss them, and in the time I had I was unable to find any helpful information. So I shall leave them out.

That brings me to the metastatic neoplasms in the mediastinum. The most common sources for these are the lungs and breast. The male breast is an uncommon source, although tumors when they occur there are highly malignant. There was no mention of this man's breast. Since Dr. Wang said that the peripheral lung fields were clear, and the cytologic examination was negative, I do not have any grounds for making the diagnosis of a small peripheral lung tumor, such as an adenocarcinoma, which would explain the clubbing. The best conclusion that I can draw, then, is that this was a metastatic neoplasm in a lymph node from a distant focus that was not unearthed.

DR. EDWARD F. BLAND: Have you ever seen an aneurysm as silent as this?

DR. PITTMAN: No.

DR. BLAND: I wonder if someone could inform us about the difference between paralysis of the left vocal cord and fixation.

DR. WILLIAM R. WADDELL: Immediately on section of a recurrent laryngeal nerve, the cord becomes flaccid and extends to the midline. Later, as the degeneration of the nerve proceeds, the cord retracts laterally and becomes fixed in abduction. Actually, from the clinical point of view, I doubt if that helps us very much. There is considerable variation among individual cases.

DR. ROBERT E. SCULLY: Dr. Waddell, what was your preoperative impression?

DR. WADDELL: Our preoperative diagnosis was carcinoma of the lung. We had in mind the x-ray findings quite as firmly as Dr. Pittman. I think her points about the reasons that this mass was not a primary carcinoma of the lung are well made. The failure to visualize a tumor of central location by bronchoscopic examination is strong evidence indeed against bronchogenic carcinoma. With the preoperative diagnosis we made one may wonder why we felt obliged to operate on the patient. First, we had no histologic diagnosis, and when other considerations allow it, an attempt should be made to establish one. Secondly, although it is generally true that vocal-cord paralysis with tumors of the lung is a sign of inoperability, in a few cases such tumors are resectable, particularly when the paralysis of the vocal cord has resulted from metastasis to a single lymph node.

CLINICAL DIAGNOSIS

Carcinoma of lung.

DR. HELEN S. PITTMAN'S DIAGNOSIS

Metastatic carcinoma of unknown origin to mediastinal lymph nodes.

Anatomical Diagnosis

Arteriosclerotic aneurysm of concavity of aortic arch.

Pathological Discussion

Dr. Waddell: When the chest was opened, the lung was found to be normal. It was immediately apparent that there was an aneurysm of the underportion of the aortic arch just below the origin of the left subclavian artery (Fig. 3). The aneurysm was

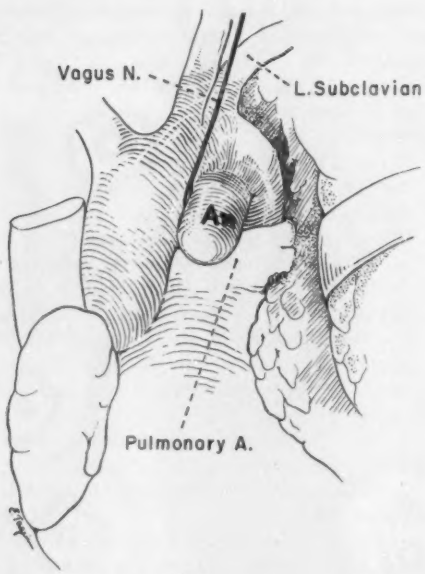

Figure 3. *Diagram, Illustrating an Aneurysm Arising from the Undersurface of the Aorta and Its Relation to the Left Vagus Nerve.*

about the size and shape of a hen's egg; its wall was extremely thin and did not pulsate. There were plaques of atherosclerosis involving several areas of the aorta, particularly about the ostia of the left carotid and left subclavian arteries. The aneurysm, which was of the saccular type, had arisen in a similar plaque. The neck of the aneurysm was small, and the tissue in that region was fairly firm in contrast to the thinned-out major portion of the sac. The dissection was extended to the point where clamps could be applied across the opening of the aneurysm. As often happens, during the dissection the aneurysm was punctured. This did not cause a hemorrhage, but 10 or 15 cc. of cloudy, thin fluid escaped. The reason for this and for the fact that the angiocardiogram failed to demonstrate the aneurysm was that there was a dense clot in its opening; it lay like a cork in the opening and was easily lifted out. The clamps were applied to the mobilized aneurysm, the sac was excised, and the opening was closed without difficulty, except that the atheroma in the region made it technically difficult to place the sutures. The patient was discharged on the tenth postoperative day.

Dr. Scully: The specimen of aneurysm wall sent to the laboratory showed severe atherosclerosis and mural thrombosis. There was complete destruction of the media, with fibrous-tissue replacement. No changes suggestive of a syphilitic etiology were seen.

Dr. Pittman: I think it is unfortunate that we could not see the angiocardiograms because the questions I asked Dr. Wang about the relation of the mass to the visualized vessels are pertinent in retrospect.

Dr. Bland: How was the nerve at operation?

Dr. Waddell: The vagus nerve was stretched out, and there was tension not only on the recurrent laryngeal nerve but also on the vagus nerve itself. We have discussed the possibility that the patient's ill health for two months was produced by traction on the vagus nerve.

Dr. Bland: A feature that interests me is whether or not the paralysis of the vocal cord cleared. It is too early, I suppose, to know. I have seen paralysis of the vocal cord of six months' duration with mitral stenosis that disappeared after commissurotomy.

Dr. Scully: Dr. Wang, how often do you see a malignant tumor that is fixed to the aortic arch appear to move with the aorta?

Dr. Wang: I think that is not an uncommon finding.

The New England Journal of Medicine

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WELCOME TO NEW ENGLAND

THE *New England Journal of Medicine* joins the medical societies of the six New England states in welcoming the American Medical Association to this historic area, stretching from the frozen muskeg of northern Maine's impenetrable forests to the golden grass of Connecticut's expansive marshes. The program of the Interim Session, in its latest available form at the time this issue of the *Journal* went to press, is published elsewhere in these pages; not only is the scientific nourishment ample, but it is supplemented by a variety of entertainment less taxing on the higher intellectual centers.

The Massachusetts Medical Society welcomes the fellows of the Association and their guests to its simple but satisfactory quarters at 22 The Fenway, overlooking Boston's famous fens. The *Journal*, established in the Boston Medical Library at 8 The Fenway, next door to the Society, in conjunction with the Library invites the same privileged persons to break the sound barrier that encloses their own series of sanctums, and stop in for a cup of coffee.

CORTISONE VERSUS ASPIRIN IN EARLY RHEUMATOID ARTHRITIS

FEW indeed are the therapeutic experiments that have been performed on significant numbers of patients allocated at random by some prearranged plan to a type of therapy and then all studied according to the same protocol. In Great Britain, however, several such studies have been carried out in recent years by specially chosen groups of well qualified investigators under the aegis of the Medical Research Council. One such study,[1] comparing cortisone and aspirin in the treatment of early cases of rheumatoid arthritis, was conducted by a joint committee of the Medical Research Council and the Nuffield Foundation on clinical trials of cortisone, ACTH and other therapeutic measures in chronic rheumatic disease.

This therapeutic trial was designed to answer a specific but important question, Is it possible, in early and uncomplicated cases of rheumatoid arthritis, to maintain the patient's well being more efficiently by treatment with cortisone than by treatment with aspirin? An opportunity was offered at the same time to study the evolution of the rheumatoid process during prolonged therapy with these two different agents. The aim was to measure the therapeutic effects on the rheumatoid process of a long-term treatment initiated while that process was still uncomplicated either by severe anatomic changes in the joints or by metabolic disturbance from a prolonged and debilitating disease.

For this purpose 61 patients regarded as suitable for treatment with either agent were admitted to 6 centers in England and Scotland; 30 were treated with cortisone and 31 with aspirin, their allocation

being made entirely at random within each center and so far as sex and duration of illness were concerned. Observations made at one, eight and thirteen weeks and approximately a year after the start of treatment showed that they had run a closely parallel course in nearly all respects — for example, in joint tenderness, strength of grip, tests of dexterity of hand and foot and clinical assessment of activity of the disease and of the patient's functional capacity. The report of the first year's observation concluded, "For practical purposes, therefore, there appears to have been surprisingly little to choose between cortisone and aspirin in the management of these 61 patients in the early stages of rheumatoid arthritis."

A further report[2] has now been made on the second year of therapy, during which treatment with one or the other agent was continuous, and "individualized" by the physician in charge of the patient to meet each patient's needs. At approximately the end of two years of treatment 58 of the original patients were reassessed clinically and subjected to some simple objective tests, with x-ray examination of their hands and feet and determination of their hemoglobin levels and sedimentation rates. In no respect did the two groups differ by more than might easily have been due to chance, and in most respects they were distinguished more by their equalities than by their differences. This report also concluded, "At the end of two years, therefore, as previously reported at the end of one year, it appears that for practical purposes there has been remarkably little to choose between cortisone and aspirin in the management of this group of patients."

This is an extraordinary commentary on the initial judgment of many outstanding physicians regarding the almost miraculous and specific efficacy attributed to the adrenocortical hormones in the rheumatic diseases. Regardless of the interpretations that the enthusiastic advocates of these remedies will put on this report and the objections that they may raise to some of the details of the study, it certainly raises serious doubts concerning the superiority of cortisone over aspirin, when both are used intelligently and the patients observed objectively. Many, though probably not all, of the possible objections to the interpretation have been considered in this report and in the editorial that appeared in the same issue. The enthusiasm for the use of adrenal hormones in many other conditions in which they are given for indications other than replacement therapy must be treated with similar and even greater skepticism, for in most of those conditions controlled data are notably lacking.

References

1. Joint Committee of the Medical Research Council and the Nuffield Foundation on Clinical Trials of Cortisone, A.C.T.H., and Other Therapeutic Measures in Chronic Rheumatic Disease. Comparison of cortisone and aspirin in treatment of early cases of rheumatoid arthritis. *Brit. M. J.* **1**:1224-1227, 1954.
2. *Idem.* Comparison of cortisone and aspirin in treatment of early cases of rheumatoid arthritis. *Brit. M. J.* **2**:695-700, 1955.

SPECIAL SERVICES HAVE THEIR DAY IN COURT

THE McKittrick report on principles of remuneration for the special services of the pathologist, roentgenologist and anesthesiologist is one of the numerous contributions by fellows of the Massachusetts Medical Society that have done much to clarify knotty controversial problems. In the most recent version of these principles, the modified "Hess Report," published as "Guides for Conduct of Physicians in Relationships with Institutions,"[1] the statement is made that a physician should not dispose of his services to any hospital under terms that permit the sale of the services of the physicians by the hospital for a fee. *The Principles of Medical Ethics of the American Medical Association,* however, which take precedence over the Guides, say (Chapter VII, Section 5) that a physician should not dispose of his services and so forth under terms that permit exploitation of the services of the physician — a subtle, but significant distinction.

An important recommendation contained in the original McKittrick report was that the medical costs of hospital care be separated from the nonmedical costs by proper methods of cost accounting, and that they appear thus separated on the statement submitted to the patient. The Council of the Massachusetts Medical Society voted in 1950 to encourage the establishment of a uniform system of hospital cost accounting in Massachusetts. By proper accounting it becomes easier to determine if exploitation is occurring — whether of the physician, the hospital or the patient.

In the state of Iowa this matter has been removed from the area of philosophic or ethical debate and is in the courts. In January, 1955, the Iowa Hospital Association asked Polk County District Court to overrule an opinion attributed to Attorney General Leo Hoegh (now Iowa's governor) that hospitals employing licensed physicians and billing patients for their services or services rendered in their departments were practicing medicine illegally. The trial began on May 19, recessed on June 28 and was resumed on September 15.

A summary of the Iowa situation may be found in the *Bulletin of the College of American Pathologists.*[2] *Hospital Management*[3,4] has summarized the point of view of the hospitals in its issues of June, July and August, 1955.

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1. Abstract of proceedings of House of Delegates at clinical session in Los Angeles, Calif., Dec. 4-7, 1951. *J.A.M.A.* **147**:1684, 1951.
2. Iowa law suit. *Bull. Coll. Am. Pathologists* **9**:4, 1955.
3. Hanna, E. J. Are non-profit hospitals breaking law? *Hosp. Management* **79**:41-46, June, 1955.
4. *Idem.* Burning question in Iowa. *Hosp. Management* **80**:52-58, 105 and 108, July, 1955.

ULTRASONIC LITHOTRESIS

As long ago as June 22, 1950, the *Journal* commented on a new technic developed at New Haven for converting large rocks into little ones — a method of lithotrity by which calculi could be reduced to calculiculi by the mere application of high-frequency sound waves.[1] The technic, almost alarming in its simplicity, was not completely dissimilar to the action of ocean waves on a rocky shore, being only of a higher frequency, neater and less noisy.

In the original experiments, according to the Yale News Bureau, which released the information, human gallstones immersed in water in a cellophane bag were subjected to a 400-kilocycle ultrasonic beam and reduced to rubble if not actually to dust. Equal success was achieved on calculi placed in exteriorized loops of rabbits' intestine and in the gall bladders of dogs, let the chips fall where they may.

So many difficulties were encountered in the further development of this ultra-modern research, however, that the investigators sought other methods of applying the supersonic source of power in such a way as to achieve the desired end with least damage to the lithiasic host. After more than five years of continued experimentation the investigators have devised a new method of tracking down and dispatching their quarry and have successfully demonstrated it — this time on stones planted in the ureters of human cadavers.

According to this technic, described by Lamport and Newman,[2] the supersonic source of energy is applied to a minute drill point with an oscillatory effect, somewhat like that of a pneumatic drill on a smaller and less turbulent scale. Transmitted to the drill tip through four ribbon wires running the length of the enclosing catheter, the sound waves at 25,000 vibrations per second give it a woodpecker's beak action with an excursion of one to two one-thousandths of an inch. Harmless to the manipulating surgeon and to surrounding soft tissues, the effect of the vibration is one that hard substances are unable to withstand.

Stones introduced into the human cadaver having been successfully fractionated by this method and animals having been experimented on without ill effects, the investigators hope that eventually its potentialities may be brought to bear on neolithic man still living.

REFERENCES

1. Editorial. Supersonic surgery. *New Eng. J. Med.* **242**:991, 1950.
2. Lamport, H., and Newman, H. F. Clinical appraisal of methods for disruption and extraction of urinary calculi, especially with ultrasound. *Yale J. Biol. & Med.* **27**:395-431, 1955.

Dying without medical aid. — *Dr. Stark, the superintendent of medical statistics to the Registrar-General, under the new act for the Registration of Births, Marriages and Deaths in Scotland, reports that forty-one out of every hundred of the people who die in Dundee, die without medical attendance. If the figures are correct, the fact is deplorable. The annual number of deaths in Dundee being 1800, more than 700 perish there without medical attendance.* — Lancet

Boston M. & S. J., *Nov. 29, 1855*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS DECEMBER, 1955

Orthopedic Clinic	Date	Clinic Consultant
Greenfield	December 1	Charles L. Sturdevant, M.D.
Lowell	December 2	Albert H. Brewster, M.D.
Salem	December 5	Paul W. Hugenberger, M.D.
Haverhill	December 7	William T. Green, M.D.
Brockton	December 8	George W. Van Gorder, M.D.
Gardner	December 12	Carter R. Rowe, M.D.
Lynn*	December 12	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Worcester	December 16	John W. O'Meara, M.D.
Fall River	December 19	David S. Grice, M.D.
Pittsfield	December 21	Edward J. Coughlin, Jr., M.D.
Hyannis	December 22	Paul L. Norton, M.D.
Springfield	December 27	James D. Fisher, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	December 6, 13, 20, 27
Fitchburg	December 7, 14, 21, 28

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

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*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Planning Florida's Health Leadership: Florida's hospitals and nurses. Vol. 4. By John Maclachlan, Ph.D. 8°, paper, 122 pp., with 44 tables. Gainesville: University of Florida Press, 1954. $1.50.

This volume summarizes the findings of the Medical Center study for the University of Florida hospitals and nursing service. The topics comprise hospital facilities, the adequacy of state hospital resources, special services, health-team training and nursing. The set of survey volumes should be in all public-health collections.

Connective Tissue in Health and Disease. Edited by G. Asboe-Hansen, M.D., Connective Tissue Research Laboratory, University Institute of Medical Anatomy, Copenhagen. 8°, cloth, 321 pp., with illustrations. Copenhagen: Ejnar Munksgaard, 1954. $7.50.

This monograph includes contributions by an international group of 23 specialists on the chemistry, physiology and pathology of connective tissue. Lists of references are appended to the papers; the publishing is excellent.

CLINICAL MEETING OF THE AMERICAN MEDICAL ASSOCIATION

Tuesday, Wednesday, Thursday and Friday, November 29 and 30 and December 1 and 2

Mechanics Building, Boston

PROGRAM

TUESDAY, NOVEMBER 29

SCIENTIFIC LECTURES AND MEETINGS

GRAND HALL

10:30 - 11:00 a.m. Frank Foster, M.D., Elliott P. Joslin, M.D., and Elmer Hess, M.D., president of the American Medical Association.

11:00 - 11:45 The Art of Medicine. C. Sidney Burwell, M.D., professor of medicine, Harvard Medical School, physician, Peter Bent Brigham Hospital, and visiting physician, Boston Lying-in Hospital.

11:45 a.m. - 12:30 p.m. Trends in Medical Research. James A. Shannon, M.D., director, National Institutes of Health, Bethesda, Maryland.

2:00 - 3:30 Clinicopathological Conference: Benjamin Castleman, M.D., clinical professor of pathology, Harvard Medical School, and chief, Department of Pathology, Massachusetts General Hospital; Charles S. Davidson, M.D., associate professor of medicine, Harvard Medical School, and associate director, Second and Fourth (Harvard) Medical Services, Boston City Hospital; Ralph E. Miller, M.D., professor of pathology, Dartmouth Medical School, and director of Laboratories, Mary Hitchcock Memorial, Hanover, New Hampshire; and Leland S. McKittrick, M.D., clinical professor of surgery, Harvard Medical School, and surgeon, New England Deaconess Hospital.

3:30 - 5:00 Panel — Antimicrobial Therapy: Chester S. Keefer, M.D., professor of medicine, Boston University School of Medicine, and physician-in-chief, Massachusetts Memorial Hospitals, moderator; Louis A. Weinstein, M.D., associate professor of medicine, Boston University School of Medicine, and chief, Department of Infectious Diseases, Massachusetts Memorial Hospitals; Maxwell Finland, M.D., associate professor of medicine, Harvard Medical School, and associate director, Thorndike Memorial Laboratory, Boston City Hospital; Chester A. Howe, M.D., assistant professor of surgery, Boston University School of Medicine, and visiting surgeon, Massachusetts Memorial Hospitals; William P. Boger, M.D., associate in medicine, University of Pennsylvania School of Medicine and Graduate School of Medicine, and director, Department of Research Therapeutics, Norristown State Hospital, Norristown, Pennsylvania; and Mark H. Lepper, M.D., professor of preventive medicine and head, Department of Medicine, University of Illinois College of Medicine, and consulting director, Respiratory Center, Research and Educational Hospital, University of Illinois.

PAUL REVERE HALL

2:00 - 3:00 Panel — Anemia: William B. Castle, M.D., professor of medicine, Harvard Medical School, and director, Thorndike Memorial Laboratory, Boston City Hospital, moderator; T. S. Evans, M.D., professor of clinical medicine, Yale University School of Medicine, and attending physician, Grace-New Haven Community Hospital and Hospital of St. Raphael; Herman A. Lawson, M.D., lecturer on medicine, Boston University School of Medicine, and chief, Medical Service, Veterans Administration Hospital, Providence, Rhode Island; Charles P. Emerson, M.D., associate professor of medicine, Boston University School of Medicine, and director, Hematology Laboratories, Massachusetts Memorial Hospitals; and William C. Moloney, M.D., professor of clinical medicine, Tufts University School of Medicine, and director, Clinical Laboratories, Boston City Hospital.

3:00 - 3:30 The Clinical Use and Anticoagulant Properties of Phenindione. Herbert S. Sise, M.D., assistant clinical professor of medicine, Tufts University School of Medicine, and director, Anticoagulant Laboratory, and junior visiting physician, Boston City Hospital; Dionysios Adamis, M.D., research fellow in medicine, Tufts University School of Medicine and Boston City Hospital; and Delbert M. Kimball, A.B., research technician, Anticoagulant Laboratory, Boston City Hospital.

3:30 - 4:00 Nitrous Oxide-Oxygen-Curare Analgesia for Major Surgery in the Poor-Risk Patient. Morris L. Heller, M.D., assistant professor in the physiologic sciences, Dartmouth Medical School; and T. Richard Watson, Jr., M.D., instructor in clinical surgery and in the physiologic sciences, Dartmouth Medical School, and director, Cardio-Pulmonary Physiology Research Laboratory, Hitchcock Foundation.

4:00 - 4:30 Nonunion of Bone. Edwin F. Cave, M.D., assistant professor of orthopedic surgery, Harvard Medical School, and chief, Fracture Service, Massachusetts General Hospital.

4:30 - 5:00 Management of "Frozen Shoulder." G. Edmund Haggart, M.D., Robert J. Dignam, M.D., and Thomas F. Sullivan, M.D., Department of Orthopedic Surgery, Lahey Clinic.

The Treatment of Checkrein Shoulder by Manipulation and Cortisone. T. B. Quigley, M.D., assistant clinical professor of surgery, Harvard Medical School, and senior associate in surgery, Peter Bent Brigham Hospital.

TALBOT HALL

2:00 - 3:00 Panel — Adolescent Medicine: Charles A. Janeway, M.D., professor of pediatrics, Harvard Medical School, and physician-in-chief, Infants' and Children's hospitals, moderator; J. Roswell Gallagher, M.D., chief, Adolescent Unit, Children's Medical Center; Dana L. Farnsworth, M.D., director, Hygiene Department, Harvard University, and associate physician, Children's Medical Center; W. Warren Point, III, M.D., assistant in medicine, Harvard Medical School and Massachusetts General Hospital; Somers H. Sturgis, M.D., associate clinical professor of gynecology, Harvard Medical School, and gynecologist-in-chief, Peter Bent Brigham Hospital; and Walter T. Goodale, M.D., instructor in medicine, Harvard Medical School, and consultant in cardiology, Adolescent Unit, Children's Hospital.

3:00 - 3:30 The Significance of a Fat-Splitting Enzyme in the Urine for the Diagnosis of Pancreatic Disease. Martin M. Nothman, M.D., assistant clinical professor of medicine, Tufts University School of Medicine; J. H. Pratt, M.D., professor of medicine, Tufts University School of Medicine; and A. D. Callow, M.D., assistant professor of surgery, Tufts University School of Medicine.

Present-Day Concepts of Anacidity. Howard M. Spiro, M.D., instructor in medicine, Yale University School of Medicine.

3:30 - 4:00 The Clinical Use of the Urinary Uropepsin Excretion in Gastrointestinal and Endocrine Diseases. Seymour J. Gray, M.D., Ph.D., assistant professor of medicine, Harvard Medical School, and Robert W. Reifenstein, M.D., Colin G. Ramsey, M.D., Vincent A. DeLuca, Jr., M.D., and Lewis J. Krakauer, M.D., of the staff of Peter Bent Brigham Hospital.

4:00 - 4:30 The Hiatus-Hernia Complex: Peptic esophagitis, stricture, hemorrhage, and anemia, Mallory–Weiss syndrome, marginal ulcer. Felix G. Fleischner, M.D., clinical professor of radiology, Harvard Medical School, and director, Department of Radiology, Beth Israel Hospital.

4:30 - 5:00 Results of Subtotal Gastric Resection (Billroth II) for Duodenal Ulcer Disease. 1. The Influence of Preoperative Acidity upon Postoperative Acidity in Relation to the Extent of Resection. 2. Relation of Postoperative Sequelae to Extent of Resection. James L. A. Roth, M.D., assistant professor of gastroenterology and physiology, Graduate School of Medicine, University of Pennsylvania; Irvin M. Becker, M.D., clinical instructor in medicine, Marquette University; Sherwood Vine, M.D., clinical assistant in gastroenterology, Graduate School of Medicine, University of Pennsylvania; and Henry L. Bockus, M.D., chairman, Department of Medicine, and professor of gastroenterology, Graduate School of Medicine, University of Pennsylvania.

Medical Color-Television Program

Television Room (second floor)

2:00 - 2:20 Diagnostic Evaluation of the Patient with Bleeding Disease. Mario Stefanini, M.D., and associates, St. Elizabeth's Hospital.

2:20 - 2:40 Hemorrhage and Thrombosis: Two sides of a coin. Benjamin Alexander, M.D., and Stanford Wessler, M.D., Beth Israel Hospital.

2:40 - 3:00 The Management of Rheumatoid Arthritis. Theodore B. Bayles, M.D., Robert Breck Brigham Hospital.

3:00 - 3:20 Treatment of Gout. Elmer C. Bartels, M.D., Lahey Clinic.

3:20 - 4:00 Clinic on Poliomyelitis. Charles A. Janeway, M.D., R. Cannon Eley, M.D., William T. Green, M.D., David S. Grice, M.D., Sidney Kibrick, M.D., and Benjamin G. Ferris, Jr., M.D., Children's Medical Center.

WEDNESDAY, NOVEMBER 30

Scientific Lectures and Meetings

Grand Hall

9:30 - 10:00 a.m. The Control of Hepatitis. Richard B. Capps, M.D., associate professor of medicine, Northwestern University.

10:00 - 10:30 The Responsibility of the Family Doctor in the Treatment of Tuberculosis. J. Burns Amberson, Jr., M.D., consultant, Chest Service, Bellevue Hospital and Presbyterian Hospital, New York City, and professor of medicine, College of Physicians and Surgeons, Columbia University.

10:30 - 11:00 The Acute Abdomen. Isidor S. Ravdin, M.D., professor of surgery, University of Pennsylvania School of Medicine, and director of the Harrison Department of Surgical Research, Medical Schools, University of Pennsylvania.

11:00 a.m. - 12:30 p.m. Panel — Psychotherapy in General Practice: Claude E. Forkner, M.D., moderator; Jackson M. Thomas, M.D., professor of psychiatry and chairman, Department of Psychiatry, Tufts University School of Medicine; Vernon P. Williams, M.D., assistant psychiatrist, Massachusetts General Hospital; Henry Brosin, M.D., director, American Board of Psychiatry and Neurology; and Carl Binger, M.D., lecturer on psychiatry, Harvard Medical School, and consulting visiting psychiatrist, Massachusetts General Hospital.

2:00 - 2:30 The Enteric Viruses. Thomas H. Weller, M.D., associate professor of tropical public health, Harvard School of Public Health, assistant director, Research Division of Infectious Diseases, and associate physician, Children's Hospital.

2:30 - 3:30 X-Ray Conference — Presentation and Discussion of Problems in Cardiac and Pulmonary Diseases: Merrill C. Sosman, M.D., professor of radiology, Harvard Medical School, and radiologist-in-chief, Peter Bent Brigham Hospital; Donald S. King, M.D., professor of thoracic medicine, Dartmouth Medical School, and physician, Hitchcock Clinic, Hanover, New Hampshire; Samuel A. Levine, M.D., clinical professor of medicine, Harvard Medical School, and physician, Peter Bent Brigham Hospital; and Richard H. Sweet, M.D., associate clinical professor of surgery, Harvard Medical School, and general and thoracic surgeon, New England Deaconess Hospital.

3:30 - 5:00 Panel — Evaluation and Management of the Surgical Risk: Arthur W. Allen, M.D., consultant in surgery, Massachusetts General Hospital, moderator; Isador S. Ravdin, M.D., professor of surgery, University of Pennsylvania School of Medicine, and director, Harrison Department of Surgical Research, Medical Schools, University of Pennsylvania; Dana W. Atchley, M.D., professor of clinical medicine, College of Physicians and Surgeons, Columbia University, and attending physician, Presbyterian Hospital, New York City; Edward F. Bland, M.D., associate clinical professor of medicine, Harvard Medical School, and chief, Cardiac Unit, Massachusetts General Hospital; John Abajian, Jr., M.D., professor of surgical anesthesia, University of Vermont; and Douglas A. Farmer, M.D., assistant professor of surgery, Boston University School of Medicine, and assistant visiting surgeon, Massachusetts Memorial Hospitals.

Paul Revere Hall

9:00 - 9:30 Pheochromocytoma — a Clinicopathological Analysis of 38 Cases. M. M. Melicow, M.D., assistant clinical professor of urology, Columbia Presbyterian Medical Center, and uropathologist, Squier Urological Clinic, Presbyterian Hospital, New York City.

9:30 - 10:00 Persistent Hyperthyroidism with Normal PBI on Antithyroid Therapy. Earle M. Chapman, M.D., assistant clinical professor of medicine, Harvard Medical School, and physician, Massachusetts General Hospital; and Farahe Maloof, M.D., assistant in medicine, Harvard Medical School and Massachusetts General Hospital.

10:00 - 10:30 Diabetes of Thirty-Five Years' Duration. Paul Barclay, M.D., fellow in medicine, New England Deaconess Hospital; and Howard F. Root, M.D., associate in medicine, Harvard Medical School, and physician, New England Deaconess Hospital.

10:30 - 11:00 On Death by Drowning. Captain Christopher C. Shaw (MC), USN., Medical Dispensary, Philadelphia Naval Shipyard.

11:00 - 11:30 The Pathogenesis of Acute Glomerulonephritis and "Lipoid Nephrosis"; Demonstration of glomerular-localizing globulins. Robert G. Mellors, M.D., and Louis G. Ortega, M.D., associate members, Sloan–Kettering Institute for Cancer Research, New York City Cornell University Medical College.

11:30 a.m. - 12:00 m. Incidence of Asymptomatic Infections of the Urinary Tract in an Outpatient Population. Edward H. Kass, M.D., Ph.D., and Egon Riss, M.D., Thorndike Memorial Laboratory, Boston City Hospital, and Department of Medicine, Harvard Medical School.

12:00 m. - 12:30 p.m. Environmental Support in Long-Term Illness. Robert P. Smith, M.D., clinical fellow in medical rehabilitation, Massachusetts General Hospital.

2:00 - 2:30 A Simple Clinical Test for Detecting the Altered Cardiodynamics of Ventricular Failure or Valvular Stenosis. John H. Knowles, Lt. (MC) USNR, and Richard Gorlin, Lt. (MC) USNR., United States Naval Hospital, Portsmouth, Virginia.

2:30 - 3:00 The Influence of Heart Disease on Surgical Risk. J. B. Dana, M.D., cardiologist, Veterans Administration Center, Togus, Maine; and R. L. Ohler,

M.D., chief, Medical Service, Veterans Administration Center, Togus, Maine.
Age, Serum Lipids and Coronary Atherosclerosis. David Adlersberg, M.D., Louis E. Schaefer, M.D., Arthur G. Steinberg, Ph.D., and Chun-I Wang, M.D., Department of Medicine, Mount Sinai Hospital, New York City.

3:00 - 3:30 Isolated Aortic Stenosis: Evaluation for surgical treatment, choice of operation and results. George B. Starkey, M.D., instructor in surgery, Harvard Medical School, assistant surgeon, Children's Medical Center, and assistant visiting surgeon, Boston City and Massachusetts Memorial Hospitals; and Walter H. Abelmann, M.D., associate in medicine, Harvard Medical School, and assistant physician, Thorndike Memorial Laboratory, Boston City Hospital.

3:30 - 4:00 The Varied Manifestations of Dissecting Aneurysm of the Aorta. Samuel Baer, M.D., senior attending physician, Albert Einstein Medical Center.

4:00 - 4:30 The Pathogenesis of Acute Peripheral Arterial Occlusion: A basis for clinical management. Stanford Wessler, M.D., associate in medicine, Harvard Medical School, and associate in medicine and medical research, Beth Israel Hospital; and Marvin Gilbert, M.D., research fellow in medicine, Harvard Medical School, and research fellow in medical research, Beth Israel Hospital.

4:30 - 5:00 Remittent Necrotizing Acrocyanosis. Edward A. Edwards, M.D., Department of Surgery, Peter Bent Brigham Hospital.

Talbot Hall

9:00 - 9:30 a.m. Practical Aspects of the Preanesthetic Management of Children in a Community Hospital. Peter G. Lehndorff, M.D., A. D. Delisle, M.D., and N. H. Stewart, M.D., Department of Anesthesiology, Burbank Hospital, Fitchburg, Massachusetts.
Another Look at Acne Vulgaris in Adolescence. William R. Hill, M.D., consultant in dermatology, Adolescent Unit, Children's Medical Center; Felix P. Heald, M.D., assistant director, Adolescent Unit, Children's Medical Center; Robert P. Masland, Jr., M.D., assistant physician, Adolescent Unit, Children's Medical Center; and J. Roswell Gallagher, M.D., chief, Adolescent Unit, Children's Medical Center.

9:30 - 10:00 The Crying Baby. David McL. Greeley, M.D., director, Clinical Services, Harlan Memorial Hospital, Harlan, Kentucky.

10:00 - 10:30 Accidental Poisoning in Children. Harold Jacobziner, M.D., assistant commissioner, Maternal and Child Health Service, Department of Health, New York.

10:30 - 11:00 Blood Replacement in Thoracic Surgery for Children. Robert M. Smith, M.D., anesthesiologist, Children's Medical Center; and Robert E. Gross, M.D., Ladd Professor of Children's Surgery, Harvard Medical School, and surgeon-in-chief, Children's Medical Center.

11:00 - 11:30 Hypothyroidism in Adolescence. Felix P. Heald, M.D., assistant director, Adolescent Unit, Children's Medical Center; Albert Renold, M.D., consultant in endocrinology, Adolescent Unit, Children's Medical Center; and J. Roswell Gallagher, M.D., chief, Adolescent Unit, Children's Medical Center.

11:30 a.m. - 12:00 m. Management of Behavior Disorders in Children. Harry Bakwin, M.D., professor of clinical pediatrics, New York University.

12:00 m. - 12:30 p.m. The Clinical Management of Phenylketonuria. David Yi-Yung Hsia, M.D., instructor in pediatrics, Harvard Medical School; Walter Troll, Ph.D., research associate, Cancer Research Institute, New England Deaconess Hospital; and W. Eugene Knox, M.D., assistant professor of biologic chemistry, Harvard Medical School.

2:00 - 2:30 Renal-Function Studies throughout Pregnancy in the Normal Woman. Kermit E. Krantz, M.D., assistant professor of obstetrics and gynecology, University of Vermont College of Medicine; and Ethan A. H. Sims, M.D., associate professor of medicine and biochemistry, University of Vermont College of Medicine.

2:30 - 3:00 Coagulation Defects in Severe intra-Partum and post-Partum Hemorrhage. Duncan E. Reid, M.D., professor of obstetrics, and head, Department of Obstetrics, Harvard Medical School; Charles C. Roby, M.D., research associate in obstetrics, Harvard Medical School; and Albert E. Weiner, M.D., assistant in obstetrics, Harvard Medical School.

3:00 - 3:30 The Repeat Cesarean — a Review of 1000 Cases. Roy J. Heffernan, M.D., assistant clinical professor of obstetrics and gynecology, Tufts University School of Medicine; and William A. Lynch, M.D., assistant professor of obstetrics and gynecology, Tufts University School of Medicine.

3:30 - 4:00 Saphenous-Vein Stripping for Varicose Veins during Pregnancy. Rodger E. Weismann, M.D., instructor in surgery, Dartmouth Medical School; and Edward W. Jenkins, M.D., resident in surgery, Hitchcock Hospital, Hanover, New Hampshire.

4:00 - 4:30 The Management of Hypertension Associated with Pregnancy. James H. Currens, M.D., associate physician, Boston Lying-in Hospital, and assistant in medicine, Massachusetts General Hospital; Duncan E. Reid, M.D., professor of obstetrics, Harvard Medical School; and John L. Newell, M.D., instructor in obstetrics, Harvard Medical School.

4:30 - 5:00 The Menopause: A review of the problem. Joseph Rogers, M.D., assistant professor of medicine in gynecology and obstetrics, Tufts University School of Medicine.

Medical Color-Television Program

Television Room (second floor)

9:00 - 10:15 a.m. Partial Gastrectomy for Peptic Ulcer. Samuel F. Marshall, M.D., Lahey Clinic.

10:15 - 11:30 Amputation for Diabetic Gangrene. Leland S. McKittrick, M.D., New England Deaconess Hospital and Massachusetts General Hospital.

2:00 - 2:20 p.m. Ileostomy Clinic. Richard Warren, M.D., and Francis D. Moore, M.D., Peter Bent Brigham Hospital.

2:20 - 2:40 Treatment of Diabetic Coma. Howard F. Root, M.D., Robert F. Bradley, M.D., and Leo P. Krall, M.D., Joslin Clinic and New England Deaconess Hospital.

2:40 - 3:00 Medical Management of Kidney Stones. Philip H. Hennenman, M.D., Massachusetts General Hospital.

3:00 - 3:20 Treatment of Cardiac Arrest in Stokes–Adams Disease, with External Electric Stimulation — That Is, "the Pacemaker." Paul M. Zoll, M.D., Beth Israel Hospital.

3:20 - 4:00 Adrenal Syndromes: Recognition and treatment. George W. Thorn, M.D., Albert E. Renold, M.D., and associates, Peter Bent Brigham Hospital.

THURSDAY, DECEMBER 1

Scientific Lectures and Meetings

Grand Hall

9:30 - 10:00 a.m. Postmenopausal Bleeding. Joe V. Meigs, M.D., clinical professor of gynecology, Harvard Medical School.

10:00 - 10:30 Reversible Uremic States. Franklin H. Epstein, M.D., assistant professor of internal medicine, Yale University School of Medicine, and associate physician, Grace–New Haven Community Hospital.

10:30 - 11:00 Atoms for Peace: A physician reports the Geneva Conference. William H. Sweet, M.D., associate clinical professor of surgery, Harvard Medical School, and associate visiting neurosurgeon, Massachusetts General Hospital.

11:00 a.m. - 12:30 p.m. Panel — Drugs, Radiation and Surgery in the Management of Cancer: J. Englebert Dunphy, M.D., professor of surgery, Harvard Medical School, and director, Sears Surgical Laboratory, Boston City Hospital, moderator; Magnus I. Smedal, M.D., chief, X-Ray Service, New England Baptist Hospital and Lahey Clinic; Henry M. Lemon, M.D., associate professor of medicine, Boston University School of Medicine, and visiting physician, Massachusetts Memorial Hospitals; Sidney C. Farber, M.D., professor of pathology, Harvard Medical School, and director of research, Children's Cancer Research Foundation; and Grantley W. Taylor, M.D., assistant clinical professor of surgery, Harvard Medical School, and visiting surgeon, Massachusetts General Hospital.

2:00 - 3:30 Clinicopathological Conference: Gustave J. Dammin, M.D., professor of pathology, Harvard Medical School, and pathologist-in-chief, Peter Bent Brigham Hospital; George V. Wright, M.D., St. Luke's Hospital, Cleveland, Ohio; Donald S. King, M.D., professor of thoracic medicine, Dartmouth Medical School, and physician, Hitchcock Clinic, Hanover, New Hampshire; Arthur T. Hertig, M.D., Shattuck Professor of Pathological Anatomy and head, Department of Anatomy, Harvard Medical School, and consultant pathologist to Boston Lying-in Hospital and Free Hospital for Women; Joe V. Meigs, M.D., clinical professor of gynecology, Harvard Medical School; and Somers H. Sturgis, M.D., associate clinical professor of gynecology, Harvard Medical School, and gynecologist-in-chief, Peter Bent Brigham Hospital.

3:30 - 5:00 Panel — Impact of Prolonged Medical Education on the Practice of Medicine: Edwin L. Crosby, M.D., director, American Hospital Association, moderator; John DeTar, M.D., St. Joseph's Mercy Hospital, Ann Arbor, Michigan; Creighton Barker, M.D., executive secretary, Connecticut State Medical Society; and Leland S. McKittrick, M.D., clinical professor of surgery, Harvard Medical School, and surgeon, New England Deaconess Hospital.

Paul Revere Hall

9:00 - 9:30 a.m. Treatment of Spontaneous Pneumothorax. Armand A. Lefemine, M.D., resident in surgery, Veterans Administration Hospital, Boston; Edward T. O'Hara, M.D., instructor in surgery, Boston University School of Medicine, and assistant in surgery, Tufts University School of Medicine; and Joseph P. Lynch, M.D., instructor in surgery, Boston University School of Medicine.

9:30 - 10:00 Lung-Function Tests: Their value in medical diagnosis and treatment. David W. Cugell, M.D., research fellow in medicine, Harvard Medical School and Thorndike Memorial Laboratory, Boston City Hospital; Walter H. Abelmann, M.D., associate in medicine, Harvard Medical School, and assistant physician, Thorndike Memorial Laboratory, Boston City Hospital; Edward A. Gaensler, M.D., research associate in medicine, Harvard Medical School, research associate, Thorndike Memorial Laboratory, Boston City Hospital, and instructor in surgery, Boston University School of Medicine; and Theodore L. Badger, M.D., assistant clinical professor of medicine, Harvard Medical School, and associate physician, Thorndike Memorial Laboratory, Boston City Hospital.

10:00 - 10:30 Chronic Obstructive Pulmonary Emphysema. Francis C. Lowell, M.D., associate professor of medicine, Boston University School of Medicine, and visiting physician, Massachusetts Memorial Hospitals; William Franklin, M.D., instructor in medicine, Boston University School of Medicine, and assistant visiting physician, Massachusetts Memorial Hospitals; Alan L. Michelson, M.D., assistant in medicine, Boston University School of Medicine; and Irving W. Schiller, M.D., assistant professor of medicine, Boston University School of Medicine.

10:30 - 11:00 Lipoid Pneumonia Simulating Lung Cancer. John L. Pool, M.D., associate attending surgeon, Thoracic Service Memorial Center, New York City; and Loton H. Rasmussen, M.D., clinical assistant in general medicine, Memorial Hospital, New York City.

The Treatment of Acute Respiratory Insufficiency. Eugene D. Robin, M.D., instructor in medicine, Harvard Medical School, and junior associate in medicine, Peter Bent Brigham Hospital; John M. Tyler, M.D., assistant in medicine, Peter Bent Brigham Hospital, and senior physician, Lemuel Shattuck Hospital; Eugene C. Eppinger, M.D., assistant clinical professor of medicine, Harvard Medical School, and physician, Peter Bent Brigham Hospital; and Don J. Weeks, M.D., assistant in otology and laryngology, Harvard Medical School, and associate in surgery, Peter Bent Brigham Hospital.

11:00 - 11:30 The Importance of Mitral Stenosis in Patients with Symptoms of Chronic Pulmonary Disease. Gordon S. Myers, M.D., associate in medicine, Harvard Medical School, and assistant physician, Massachusetts General Hospital; Edward F. Bland, M.D., associate clinical professor of medicine, Harvard Medical School, and physician and chief, Cardiac Clinics and Laboratory, Massachusetts General Hospital; Allan L. Friedlich, M.D., instructor in medicine, Harvard Medical School, and assistant physician, Massachusetts General Hospital; and J. Gordon Scannell, M.D., clinical associate in surgery, Harvard Medical School, and associate visiting surgeon, Massachusetts General Hospital.

11:30 a.m. - 12:00 m. Empyema in Infants and Children. Donald B. Miller, M.D., associate professor of thoracic surgery, University of Vermont College of Medicine, and attending thoracic surgeon, Mary Fletcher Hospital, Burlington; and R. James McKay, Jr., M.D., professor of pediatrics, University of Vermont College of Medicine, and chief of pediatrics, Mary Fletcher Hospital, Burlington.

Empyema Thoracis in the Antibiotic Era. Joseph P. Lynch, M.D., assistant clinical professor of surgery, Tufts University School of Medicine, and surgeon-in-chief, thoracic surgery, St. Elizabeth's and Carney hospitals; and Gerard Desforges, M.D., clinical instructor in surgery (thoracic), Tufts University School of Medicine.

12:00 m. - 12:30 p.m. Postgraduate Medical Education in the Nonuniversity Hospital. John C. Leonard, M.D., associate clinical professor of medicine, Yale University School of Medicine, and director of medical education, Hartford Hospital.

2:00 - 3:00 Panel — Industrial Medicine: Harriet L. Hardy, M.D., assistant clinical professor of preventive medicine, Harvard Medical School, and associate physician, Occupational Medical Clinic, Massachusetts General Hospital, moderator; George Morris, M.D., instructor in industrial toxicology, Boston College School of Nursing; Karl Benedict, M.D., medical director, Norton Company, Worcester, Massachusetts; Albert Seeler, M.D., clinical associate in medicine, Harvard Medical School, and associate physician, Mount Auburn Hospital; and Donald O. Hamblin, M.D., medical director, American Cyanamid Company, New York City.

3:00 - 3:30 Open Wounds of the Hand. J. Edward Flynn, M.D., assistant clinical professor of surgery, Tufts University School of Medicine.

3:30 - 4:00 Skin Grafts for Chronic Open Wounds of the Lower Extremity. Joseph E. Murray, M.D., instructor in surgery, Harvard Medical School, and associate in surgery, Peter Bent Brigham Hospital; and Bradford Cannon, M.D., clinical associate in surgery, Harvard Medical School, and associate visiting surgeon, Massachusetts General Hospital.

4:00 - 4:30 The Surgical Treatment of Abdominal Aortic Aneurysm. David P. Boyd, M.D., Department of Surgery, Lahey Clinic.

4:30 - 5:00 Evaluation of Induced Hypotension in Craniotomy. Valentino D. B. Mazzia, M.D., instructor in surgery, Cornell University Medical College, and assistant attending anesthesiologist, New York Hospital; Bronson S. Ray, M.D., professor of clinical surgery, Cornell University Medical College, and chief, Department of Neurosurgery, New York Hospital; and Joseph F. Artusio, Jr., M.D., associate professor of surgery, Cornell University Medical College, and attending anesthesiologist in charge, New York Hospital.

Talbot Hall

9:00 - 9:30 a.m. Cerebral Arteriosclerosis. Naomi Raskin, M.D., senior physician and pathologist, Boston State Hospital; and Ruth Ehrenberg, M.D., senior physician, Boston State Hospital.
Senile Degenerations of the Brain and Their Relation to Psychoses and Diseases. George Strassmann, M.D., clinical instructor, Department of Psychiatry, Tufts University School of Medicine.

9:30 - 10:00 The Administration of Anticoagulant Drugs in the Prevention and Treatment of Certain Types of Strokes. C. H. Millikan, M.D., R. G. Siekert, M.D., J. P. Whisnant, M.D., and R. M. Shick, M.D., Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota.

10:00 - 10:30 Prognostic Studies in Cerebral Palsy. Eric Denhoff, M.D., medical director, Meeting Street School for Cerebral Palsy, Providence, Rhode Island, and director of laboratory research, Emma Pendleton Bradley Home; Raymond H. Holden, M.A., clinical psychologist, Meeting Street School for Cerebral Palsy, Providence, Rhode Island; and Maurice L. Silver, M.D., chief, Neurosurgical Service, Miriam Hospital, Providence, Rhode Island.

10:30 - 11:00 Clinical Significance of Cerebral Light Sensitivity in Hereditary Light-Sensitive Epilepsy and the Encephalopathy of Uremia. C. Wesley Watson, M.D., neurologist, Department of Neurology, New England Center Hospital; Sherwood Davidson, M.D., research fellow, Department of Neurology, New England Center Hospital; and John F. Sullivan, M.D., neurologist-in-chief, Department of Neurology, New England Center Hospital.

11:00 - 11:30 Clinical Observations of Manic-Depressive Disease (A Quantitative Study of 100 Manic-Depressive Patients and 50 Medically Sick Controls). Walter L. Cassidy, M.D., instructor in psychiatry, Tufts University School of Medicine; Norris B. Flanagan, M.D., assistant professor of psychiatry, Tufts University School of Medicine, and director, Psychiatric Service, St. Elizabeth's Hospital; Marie Spellman, A.B., research assistant, St. Elizabeth's Hospital; and Mandel E. Cohen, M.D., psychiatrist, Boston Lying-in Hospital, and director, Physiologic Stress Laboratory, Massachusetts General Hospital.
A Report of 5 Deaths in Electrotherapy with Necropsy Findings in 4 of the Cases. Saunders P. Alexander, M.D., supervising psychiatrist, Rockland State Hospital, Orangeburg, New York; Lawrence H. Gahagan, M.D., Ph.D., formerly, consultant in psychiatry, United States Public Health Service; and William Hall Lewis, Jr., M.D., consulting cardiologist, Rockland State Hospital, Orangeburg, New York, and Doctors Hospital, New York City, and assistant attending physician, Memorial Center for Cancer and Allied Diseases, New York City.

11:30 a.m. - 12:00 m. Five-Year Follow-up of Patients Subjected to Three Different Lobotomy Procedures. Norman Paul, M.D., Edward Fitzgerald, M.A., and Milton Greenblatt, M.D., Department of Psychiatry, Harvard Medical School and Boston Psychopathic Hospital.

12:00 m. - 12:30 p.m. Occupational Stress and Emotional Illness. Jackson A. Smith, M.D., professor of psychiatry, University of Nebraska College of Medicine.
Compliancy Factor in Obesity and Skinniness. Adelaide M. Johnson, M.D., professor of psychiatry, Mayo Foundation and University of Minnesota; and S. Frazier, M.D., M. Griffin, M.D., and M. Faubion, M.D.

2:00 - 3:00 Panel — Seizures: Joseph M. Foley, M.D., assistant professor of neurology, Harvard Medical School, and assistant visiting neurologist, Boston City Hospital, moderator; Harry L. Kozol, M.D., clinical associate in neurology, Harvard Medical School, and visiting neurologist, Boston City Hospital; C. Wesley Watson, M.D., assistant professor of neurology, Tufts University School of Medicine, and neurologist, New England Center Hospital; and Robert S. Schwab, M.D., assistant clinical professor of neurology, Harvard Medical School, and director, Brain Wave Laboratory, Massachusetts General Hospital.

3:00 - 3:30 Serious Complications Due to Trauma of the Occiput. Robert G. Fisher, M.D., instructor in neurosurgery, Dartmouth Medical School, and neurosurgeon, Hitchcock Clinic; and Jung K. Kim, M.D., resident in neurosurgery, Hitchcock Hospital, Hanover, New Hampshire.

3:30 - 4:00 Evaluation of Thymectomy in Myasthenia Gravis. Henry R. Viets, M.D., Department of Neurology, Massachusetts General Hospital; and Robert S. Schwab, M.D., assistant clinical professor of neurology, Harvard Medical School, and director, Brain Wave Laboratory, Massachusetts General Hospital.

4:00 - 4:30 The Care of the Bladder in Neurologic Disorders. Herbert S. Talbot, M.D., chief of paraplegia and urology, Veterans Administration Hospital, West Roxbury, Massachusetts.

4:30 - 5:00 Sound-Projection Testing of Emotionally Ill U. S. Naval Personnel. H. A. Wilmer, Lt. Comdr. (MC), USNR, assistant professor of psychiatry, Stanford University; D. C. Gaede, Capt. (MC), USN, and D. Briggs, Lt. (MC), USNR.

Medical Color-Television Program

Television Room (second floor)

9:00 - 10:15 a.m. Pulmonary Resection. Richard H. Overholt, M.D., New England Deaconess Hospital.

10:15 - 11:15 Cholecystectomy and Choledochostomy. Herbert D. Adams, M.D., Lahey Clinic.

11:15 a.m. - 12:00 m. Symposium on Management of Anesthetic Emergencies; Urban H. Eversole, M.D., and staff, Lahey Clinic; Leo Hand, M.D., and staff, New England Deaconess Hospital.

2:00 - 2:20 p.m. Drug Treatment of Hypertension. Robert W. Wilkins, M.D., Massachusetts Memorial Hospitals.

2:20 - 2:40 Diagnosis and Treatment of Common Skin Diseases. Bernard Appel, M.D., Boston City Hospital.

2:40 - 3:00 Gastric Ulcer: Diagnosis and treatment. Merrill C. Sosman, M.D., and Seymour J. Gray, M.D., Peter Bent Brigham Hospital; and Samuel F. Marshall, M.D., Lahey Clinic.

3:00 - 3:30 Medical Care and Rehabilitation of the Aged and Chronically Ill. Freddy Homburger, M.D., and Charles D. Bonner, M.D., Tufts University School of Medicine and Holy Ghost Hospital.

3:30 - 4:00 Treatment of Psychiatric Patients in a General Hospital with Demonstration of Electric-Shock Treatment and Presentation of a Lobotomy Case. Robert E. Fleming, M.D., and Oscar J. Raeder, M.D., New England Deaconess Hospital; and Walter I. Tucker, M.D., Lahey Clinic.

FRIDAY, DECEMBER 2

Scientific Lectures and Meetings

Grand Hall

9:30 - 10:00 a.m. The Management of Acute Cerebrovascular Disease. Raymond D. Adams, M.D., associate clinical professor of neurology, Harvard Medical School, and chief, Neurological Service, Massachusetts General Hospital.

10:00 - 10:30 The Causes and Prevention of Congenital Anomalies. Theodore H. Ingalls, M.D., associate professor of epidemiology, Harvard School of Public Health; associate physician, Children's Medical Center.

10:30 - 11:00 The Epidemiology of Cardiovascular Disease. Paul D. White, M.D., executive director, National Advisory Heart Council, and formerly, clinical professor of medicine, Harvard Medical School.

11:00 a.m. - 12:30 p.m. Panel — Cortisones in the Treatment of Infectious, Arthritic, Malignant and Degenerative Diseases: Randall G. Sprague, M.D., professor of medicine, Mayo Foundation, Rochester, Minnesota, moderator; Benedict F. Massell, M.D., assistant clinical professor of pediatrics, Harvard Medical School, and research director, House of the Good Samaritan; Joseph J. Bunim, M.D., National Institute of Arthritis and Metabolic Diseases; Olaf F. Pearson, M.D., associate professor of medicine, Cornell University Medical College; and Wallace E. Herrell, M.D., consultant in medicine, Lexington Clinic, attending physician, St. Joseph Hospital, and Chairman of Medicine, Central Baptist Hospital, Lexington, Kentucky.

Paul Revere Hall

9:00 - 9:30 a.m. Prediction of the Response to Radioiodine Treatment for Hyperthyroidism. Belton A. Burrows, M.D., assistant professor of medicine, Boston University School of Medicine, director, Radioisotope Unit, Boston Veterans Administration Hospital, associate member, Robert Dawson Evans Memorial, and associate visiting physician, Massachusetts Memorial Hospitals; Marvin L. Mitchell, M.D., staff physician and director, Radioisotope Unit, Lemuel Shattuck Hospital; Elisabeth A. Dell, B.A., biochemist, Radioisotope Unit, Boston Veterans Administration Hospital; Dorothy A. Graham, B.S., biochemist, Radioisotope Unit, Boston Veterans Administration Hospital; and Joseph F. Ross, M.D., professor of medicine and associate dean, University of California at Los Angeles Medical School.

9:30 - 10:00 Common Emergencies in the Care of the Critically Ill: The airway, blood volume and renal function. Francis D. Moore, M.D., Moseley Professor of Surgery, Harvard Medical School, and surgeon-in-chief, Peter Bent Brigham Hospital.

10:00 - 10:30 The Management of Idiopathic Thrombocytopenic Purpura. Milton S. Sacks, M.D., professor of clinical medicine, University of Maryland School of Medicine; and Alice M. Band, M.D., instructor in medicine, University of Maryland School of Medicine.

10:30 - 11:00 Hepatic Coma. Sheila Sherlock, M.D., and W. H. J. Summerskill, M.D.

11:00 - 11:30 The Treatment with Sodium Phytate of Hypercalcemia and Hypercalcuria in Sarcoid, Hypervitaminosis D and Idiopathic Hypercalcuria. Philip H. Henneman, M.D., Evelyn L. Carroll, A. B., and Fuller Albright, M.D., Medical Clinic, Massachusetts General Hospital, and Department of Medicine, Harvard Medical School.

11:30 a.m. - 12:00 m. Hypersensitivity As a Mechanism in Vasculitis. Robert P. McCombs, M.D., professor of graduate medicine, Tufts University School of Medicine, and senior physician, New England Center Hospital; James F. Patterson, M.D., assistant professor of medicine, Tufts University School of Medicine, and physician, New England Center Hospital; and H. Edward MacMahon, M.D., professor of pathology, Tufts University School of Medicine, and pathologist, New England Center Hospital.

12:00 m. - 12:30 p.m. Physical and Physiologic Clues in Diagnosis of Eczema. Walter C. Lobitz, Jr., M.D., assistant professor of dermatology and syphilology, Dartmouth Medical School, and Dermatologist, Hitchcock Clinic; and Richard L. Dobson, M.D., resident in dermatology, Hitchcock Hospital, Hanover, New Hampshire.

Talbot Hall

9:00 - 9:30 a.m. The Interpretation of the Vaginal Smear in the Diagnosis of Cervical Cancer: Sensitivity versus specificity. Joseph E. Porter, M.D., Department of Pathology, Maine General Hospital, Portland.

9:30 - 10:00 New Laboratory Procedures Useful for the Diagnosis of Cancer of the Prostate and Cancer of the Cervix. F. Homburger, M.D., research professor of medicine, Tufts University School of Medicine; S. C. Kasdon, M.D., associate clinical professor of gynecology and obstetrics, Tufts University School of Medicine; C. D. Bonner, M.D., instructor in medicine, Tufts University School of Medicine; and W. H. Fishman, Ph.D., research professor of biochemistry and nutrition, Tufts University School of Medicine.

10:00 - 10:30 Mammary Cancer: Selection of hormone-dependent tumors using urinary estrogen and calcium studies. Andrew G. Jessiman, M.D., assistant in surgery and Henry E. Warren Fellow, Harvard Medical School, and junior associate in surgery, Peter Bent Brigham Hospital.

10:30 - 11:00 Prolonged Remissions of Advanced Mammary Cancer after Cortisone Therapy. H. M. Lemon, M.D., associate professor of medicine, Boston University School of Medicine.

11:00 - 11:30 Surgical Management of Pulmonary Metastases. John W. Strieder, M.D., professor of clinical surgery, Boston University School of Medicine, and surgeon-in-chief for thoracic surgery, Boston City Hospital and Massachusetts Memorial Hospitals.

11:30 a.m. - 12:00 m. Fifty Lung-Cancer Five-Year Survivors. Richard H. Overholt, M.D., clinical professor of surgery, Tufts University School of Medicine.

12:00 m. - 12:30 p.m. Cancer of the Colon and Rectum: A statistical and end-result study. Neil W. Swinton, M.D., and Russell L. Counts, M.D., Department of Surgery, Lahey Clinic.

Medical Color-Television Program

Television Room (second floor)

9:00 - 10:15 a.m. Abdominoperineal Resection for Carcinoma of the Rectum. Richard B. Cattell, M.D., Lahey Clinic.

10:15 - 11:30 Carcinoma of the Stomach. Richard H. Sweet, M.D., New England Deaconess Hospital and Massachusetts General Hospital.

Motion-Picture Presentation

On Tuesday, November 29, from 10:30 a.m. to 5:30 p.m., on Wednesday, November 30, and Thursday, December 1, from 9:00 a.m. to 5:30 p.m., and on Friday, December 2, from 9:00 a.m. to 12:30 p.m., medical motion pictures will be presented in Mechanics Building. A new approach in audiovisual education will be embodied in a symposium on the effectiveness of adrenalectomy for cancer of the breast on Wednesday at 11:00 a.m. On the same day, at 1:30 p.m., an audience-participation panel on the extended operation for rectal cancer will be presented. On Wednesday night, at 8:30 in the Hotel Statler, Dr. George T. Pack will present and discuss a motion picture demonstrating total right hepatic lobectomy for cancer.

NOTICES

MASSACHUSETTS HEART ASSOCIATION

The second in the series of "Stump the Cardiologist" meetings given by the Massachusetts Heart Association will be held in the Jimmy Fund Auditorium, 35 Binney Street, Boston, Wednesday, December 7, at 8 p.m.

Dr. Samuel A. Levine will give a talk entitled "New Treatment of Arrhythmias," and will invite unsigned questions from the audience. Moderators will be Drs. Harold F. Brown and Franklin K. Paddock.

PAN AMERICAN CONGRESS OF OPHTHALMOLOGY

The fifth Pan American Congress of Ophthalmology will be held in Santiago, Chile, January 9 through 14, 1956. The Congress will be under the auspices of the Pan American Association of Ophthalmology, and in accordance with the custom of inviting a distinguished ophthalmologist of the host country to preside, Dr. Cristobal Espildorá Luque, Santiago, will be president.

The program will consist of eleven symposiums. Further information may be obtained from Dr. James H. Allen, 1430 Tulane Avenue, New Orleans, Louisiana, or Dr. Daniel Snydacker, 109 Wabash Avenue, Chicago 3, Illinois.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 27 and 28. American College of Chest Physicians. Page 578, issue of September 29.

NOVEMBER 28. New England Diabetes Association. Page 886, issue of November 17.

NOVEMBER 28. Alpha Omega Alpha. Page 886, issue of November 17.

NOVEMBER 29. Boston University School of Medicine Alumni Association. Page 886, issue of November 17.

NOVEMBER 29–DECEMBER 2. American Medical Association Clinical Meeting. Mechanics Building, 111 Huntington Avenue, Boston.

NOVEMBER 29 and DECEMBER 6, 13 and 20. Boston City Hospital House Officers' Association. Page 793, issue of November 3.

NOVEMBER 30, 1955, and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

DECEMBER 1 and 2. New York University—Bellevue Medical Center. Page 840, issue of November 10.

DECEMBER 1–28. Consultation Clinics for Crippled Children in Massachusetts. Page 938.

DECEMBER 5, 1955, and JANUARY 16, 1956. Hartford Medical Society. Page 708, issue of October 20.

DECEMBER 5, 1955, and JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

DECEMBER 5–14, 1955, and JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

DECEMBER 7. Massachusetts Heart Association. Notice above.

DECEMBER 7, 1955, and JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.

DECEMBER 7, 1955–MAY 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

DECEMBER 9 and 10. Association for Research in Nervous and Mental Disease. Page 745, issue of October 27.

DECEMBER 14, 1955, and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.

DECEMBER 15. Arthritis Study Unit. Page 668, issue of October 13.

JANUARY 9–14, 1956. Pan American Congress of Ophthalmology. Notice above.

JANUARY 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 1

THURSDAY, DECEMBER 1

*American Medical Association Clinical Meeting. Mechanics Building, 111 Huntington Avenue, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m. Thoracic Conference. The Clinical Application of Pulmonary-Function Studies. Dr. John B. Petter. Main Amphitheater, Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, DECEMBER 2

*American Medical Association Clinical Meeting. Mechanics Building, 111 Huntington Avenue, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, DECEMBER 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten and staff. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, DECEMBER 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward H. MacMahon. Stearns Auditorium, New England Center Hospital.
*8:30 p.m. Fried Lecture Series. Hepatic Coma, Its Causes, Precipitating Factors and Management. Dr. Franz Ingelfinger. Usen Auditorium, Newton-Wellesley Hospital.

TUESDAY, DECEMBER 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room. Carney Hospital, Dorchester.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Medical Clinicopathological Conference. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. Portal Systemic Encephalopathy in Liver Disease. Dr. Edward Kass. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, DECEMBER 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Concluded on page xviii)

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Genito-urinary disorders	23	74%
Postoperative nausea and vomiting	15	90%
Nausea and vomiting of pregnancy	7	71%
Gall bladder disorders	10	80%

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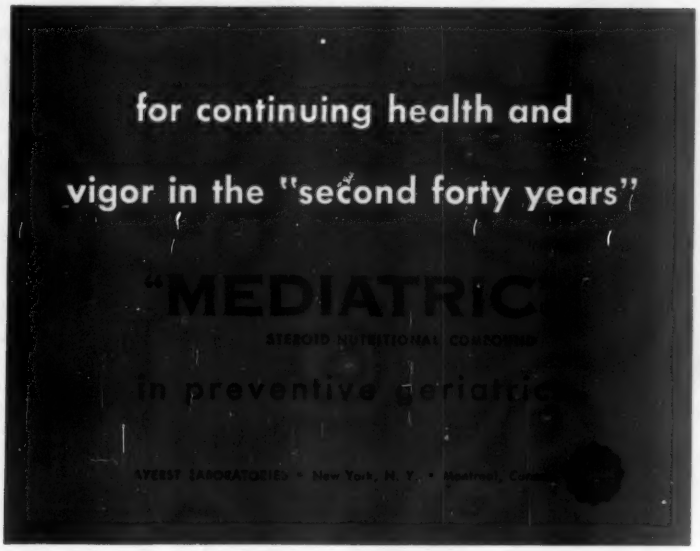

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(Concluded from page 944)

*11:00 a.m. Boston State Hospital Psychiatry Seminar. Psychiatric Consultation Service in a General Hospital. Dr. Carl Binger. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*11:00 a.m.–1:00 p.m. Postgraduate Medical Institute. Infections of Respiratory and Urinary Tracts. Drs. Reyersbach and Ross. Lowell General Hospital, Lowell.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. Bertram Selverstone, John F. Sullivan and Justin Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*2:00–4:00 p.m. Postgraduate Medical Institute. The Patient with Obstructive Emphysema or Pulmonary Fibrosis. Drs. Abelmann and Selverstone. Norfolk County Hospital, Braintree.
*2:00–4:00 p.m. Postgraduate Medical Institute. New Developments in the Management of Congestive Failure. Drs. Bloomfield, Ellis and Hamilton. Lemuel Shattuck Hospital, 170 Morton Street, Jamaica Plain.
*2:00–4:00 p.m. Postgraduate Medical Institute. Anemia. Dr. Dameshek, chairman. St. Luke's Hospital, New Bedford.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*4:00–6:00 p.m. Postgraduate Medical Institute. Management of Allergic Rhinitis and Bronchial Asthma. Drs. Burrage and Schiller. St. Luke's Hospital, Pittsfield.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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